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# ENDOCRINOLOGY:

## *The BULLETIN of the ASSOCIATION for the STUDY of the INTERNAL SECRETIONS.*

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# ENDOCRINOLOGY:

*The BULLETIN of the ASSOCIATION for the STUDY of the INTERNAL SECRETIONS*

*APRIL, 1917*

## EDITORIAL ARTICLES

### THE GROWING INTEREST IN ENDOCRINOLOGY

NATURALLY those interested in the work and objects of the Association responsible for the publication of this periodical, are more intimately in touch with the work and literature relating to the endocrine glands than others whose particular attention may not have been drawn especially to this fascinating subject.

To those who read that part of current medical literature which either is directly concerned with endocrinology or is related to it in some way, it is very evident that the number of investigators that are occupying themselves with the numerous problems in this field, is increasing considerably. In addition to this a large share of the profession is coming to realize as never before, the intimacy of the endocrine glands with many a syndrome previously

not considered to be connected with these organs. The fact remains, nevertheless, that "the endocrinous system exerts an influence on anomalies of growth, morphogenesia and organic metabolism, on nutrition and the inherent excitability of the nervous system, and on resistance to infections and intoxications, and also that it has a preponderating influence on the causation of dyscrasias and morbid temperaments." (Quoted from a report of a special committee on the ductless glands made to the Italian Society of Medicine, Rome, October, 1912.)

It is indeed well that the attention of the medical profession seems to be veering in this direction at this time, for since these factors enumerated above cannot but be of paramount interest to every physician, and obviously are intertwined with almost every manifestation in clinical medicine, the necessity for appreciating the real and prospective relations of the hormones is made doubly clear.

The more one allows the fundamental principles brought out by the intensive study of functional pathology to influence his practice, the greater will be his respect for the endocrine glands and the methods of diagnosis and treatment which our increased knowledge of them makes possible.

Now that a concerted effort is being made by so many physicians and investigators in many lands to study endocrinology, and in these pages one may find a fairly comprehensive review of the work being done in this line, it is not unreasonable to predict still greater advances in this branch of medicine; and not the least of these will result from the clinical application of this new knowledge.

## NEUROLOGICAL ASPECTS OF ENDOCRINOLOGY

FORMAL organic neurology is of intense academic interest to those who delight in solving to the last degree intricate problems. It is a subject replete with the intensive thought and deductive reasoning necessary in demonstrating a mathematical theorem. And like it, when the demonstration is completed, the finished neurological diagnosis is a thing fit for the filing cabinet or the text-book and we can look back upon the deductive processes through which we have come as delightful mental exercises.

But it leaves the human factor—the patient—much as we found him. We have learned something, but we have helped little. The indictment that the "neurologist knows most about his patient and does the least for him" has some basis in fact. Our attitude towards neurological problems has been wrong. It has been academic. It has accepted clinical pictures as disease entities with well-known anatomical structural changes in the nervous system. And structural change in the nervous system is coterminous with incurability. Our work ceased when we had decided the extent and location and nature of this structural change. Of late, our friend, the spirochete, recognized as the instigator of much of this structural change in the nervous system, has been followed and hounded out of his retreats, and it is reported as a result that many of our cases have not only been "arrested" but have gone to cure. But how few of us have thought and inquired into the reason for this reaction of the nervous system to the spirochete? Why do not all infected with syphilis become tabetic or paretic? Why do some, exposed to the same in-

fective active source as others who acquire syphilis, remain immune? In a family of whom three adults acquired syphilis from three different sources, all three became tabetic. Is it more reasonable to assume that the strain of spirochete was the same in each instance, or that the reaction of three brothers to the spirochete was familial in type? These three brothers were all undersized, showed emotional instability, abnormal hairy distribution, and were fairly well marked dyspituitarics. They had these characteristics before acquiring syphilis. One sister, non-syphilitic, was a dyspituitary epileptic. Their father attempted suicide, one brother committed suicide, while another brother also attempted it. They were all temperamentally unfit, and maladjusted. Other authors have published the coincidences seen in tabes and in pituitary disturbance. If the nervous structure of some types of dyspituitarism has not the power of resistance to certain infective agents, notably the spirochete, can we not confer that power upon it by endocrine therapy? That is the neurological problem of syphilis,—an immunological one.

Again, the large class of muscular dystrophies has gone through the decades with each investigator adding a new sub-class, a different age incidence, a new theory. The resemblance in all classes of these dystrophies—the symptoms referable to endocrine disturbances which they all show—had almost entirely escaped comment or was dismissed as a curious coincidence; and yet here was the solution. Only within the past year has an attempt been made to give due weight to such endocrine disturbances in the pathogenesis of the muscular dystrophies.* When our ef-

*Elsewhere in this issue will be found mention of such an attempt made by the writer.

forts in this direction finally shall have attained success, an efficient therapy in this difficult class of disorders is but a little beyond.

A recent, and as yet unpublished, report of the number of endocrine cases in 1000 defective children is given as 170. To have had 17 per cent. recognized as endocrine, is in itself noteworthy. The real number is probably higher. Here is a field for the neurologist's most fruitful endeavor. The Binet-Simon age of defective children, as a result of the administration of thyroid and pituitary therapy, has been advanced by years in a few months' treatment.

To refer to the mental symptoms and reactions of individuals with disturbed endocrine systems is supererogatory. Our hyperthyroids with their incessant psycho-motor activity, their lack of mental poise; the sluggishness and torpor of the hypothyroid; the insufficiency, fatigability and depression of the hypoadrenal neurasthenic; the phobias, compulsion and anxiety neuroses of the gonad involutionary period; the poise and mental power accompanying the milder hyperpituitary state,—all these need but to be mentioned to understand at a glance how the disturbances in the endocrine system make for variations in the adjustment of the individual to his surroundings and hence in his adaptability to society.

The effect, further, of the component action of the internal secretions upon the various parts of the autonomic nervous system is only now beginning to engage our attention. Surgeons operating as a cause for persistant vomiting, now for appendicitis, now for gall stone, again for stomach ulcer, and with nonsuccess, are beginning to feel the truth of the theories put forth to account for this intractable vomiting

as the basis of irritability of the cranio-bulbar division of the autonomic system—vagotonia. When such vomiting is treated on this pathogeny, it ceases.

Finally, hyperplastic conditions have of late received more and more attention from neurologists. There seems to be increasing evidence that stimulation of the thoracic autonomic system—the so-called sympathetic—gives rise to increase of tissue cells in the organ to which the stimulated fibre passes. Evidence gained from animal experimentation, the action of the internal secretions, especially of the hypophysis, on mouse and other tumors, increasing the rapidity of their growth, points to a nervous mechanism in control of hyperplasias stimulated by the endocrine glands. Might it be too much to hope that in the not too-distant future, hypoplasias may be similarly produced, and an inhibiting control of tumor growth arise?

So we see that in the new preventive neurology a field is broadening—due to the recognition of the effect of the internal glandular system on the various nervous mechanisms—that embraces wider and wider territory and whose limiting horizon is not yet fixed. It bears as little relation to the old narrow orthodox, formal neurology, as does modern medicine to the conception of disease entities of a half century ago.

Neurology, therefore, must emerge from its laissez faire position and assume the duties which endocrinology forces upon it. It must assume the place in preventive medicine that has been opened for it.

WALTER TIMME.

## THE MAMMAE AS ENDOCRINE ORGANS

THAT the mammary glands have a dual function is not yet altogether accepted by physiologists or clinicians in general. Evidence, both experimental and clinical, is gradually accumulating to indicate that the mammae may have an endocrine function; but this evidence is not as concise and unimpeachable as might be desired. The whole matter still must be considered as sub judice.

With the growing appreciation of the internal secretory value of many parts of the body, not a few of which are well known to have a dual secretory function—both internal and external, and the intimacy of the mammary glands with other organs of internal secretion (especially the ovaries, pituitary and possibly the thyroid) it may not be amiss to recall a number of the indications that lead some to believe with us that the mammary glands are indeed a part of the endocrine system, and that this phase of their functional activities is deserving of study and the resulting knowledge of much wider clinical application.

First it is clear to all that the functional activity of the mammary glands is influenced by numerous hormonic means, for their occasional transient functional activity at birth (in the production of the so-called "witches' milk"), their growth at puberty, their frequent "sympathetic association" with the menses, their relation to the sex manifestations and last, and most important of all, their response to chemical stimuli obviously of intrauterine origin, surely constitutes a series of phenomena very similar to, if indeed not actually due to, internal secretory reactions.

Not so long ago Schil selected the manifestations

of mammary evolution and physiology as the basis of a masterly study (These de Nancy, 1912) and therein sets forth his conclusions that mammary evolution is properly divided into six stages: (1) The stage of development, divided into an organogenetic phase and a phase in which there is secretory activity (the lactation in the new-born already mentioned). This is believed to be due to a hormone passing from the mother which also probably is concerned in activating mammary secretion in the mother. (2) The prepubertial stage of functional inactivity. (3) The stage of puberty, characterized by a considerable increase in glandular parenchyma which is dependent upon the maturation of the corpora lutea and obviously the result of internal secretory activities.* (4) The gravid stage, divided into the early period during which the glands attain their full development and a "phase glandulaire gravidique" which follows complete development and is characterized by secretory activity (colostrum). It is suggested that the first part of this stage is controlled by the corpus luteum of pregnancy through a hormone produced in it, while the latter part results from a chemical messenger from the fetus itself, the placenta or possibly a myometrial gland. (5) The postpartum stage includes the period of lactation initiated during pregnancy by an endogenous stimulus and maintained by mechanical means—nursing. The phase of post-

*It has been repeatedly demonstrated that the ovaries influence mammary development. For instance Bouin and Ancel (Jour. de physiol. et de pathol. general; 1911, xiii, 31) showed that ovariotomy resulted in a practical disappearance of the mammae, while on the successful grafting of a piece of ovary, the lost glands reappeared. Again O'Donoghue (Jour. Physiol. 1911, xliii, p. xvi) and others have ruptured the ripe Graafian follicles artificially, thereby making a noticeable increase both in mammary growth and activity.

partum retrogression is merely due to an absence of stimuli. Finally there is (6) the senile stage, associated with involution, and corresponding to the period when the gonads atrophy and their stimuli no longer are active.

All these comparatively well known facts serve to emphasize the interrelation of the mammary glands with endocrine function and while this evidence is none too positive, for it does not prove these glands to have an internal secretion, at least it classes them intimately with other organs known to have distinct endocrine function.

Occasionally our knowledge of the physiological activity of a given endocrine organ has resulted from its experimental removal or, more often, from the administration of extracts of it. The internal secretory character of the pituitary was demonstrated in this manner by Schaefer and his associates in 1895. Practically all the clinical value of the adrenal medullary principle resulted from gland feeding, though, of course, much physiological work has been done in other ways. Be this as it may, mammary gland feeding is not without its influence upon the organism, and in addition to a homostimulant action which is to be expected on general principles, it is of interest to recall that the chief organs affected by prolonged mammary therapy are the ovaries.

Numerous reports indicate that mammary extract exerts an antagonist effect upon ovarian endocrine activity, and its use in hyperovarism, menorrhagia and even fibroids seems to have been accompanied by indubitable results. The writings of Bell, Shober, Feodoroff, Battuaud, Luncz, Carnot and a number of

others* seem to contain within them sufficient clinical proof that this remedy is not without clinical value. We have had occasion to prescribe it in, perhaps, forty cases and the results have confirmed our belief that there is a principle in mammary substance which antagonizes ovarian activity, reduces pelvic congestion and stops local bleeding. One case recently demonstrated this unusually well: A well advanced and inoperable carcinoma uteri, which was the source of constant hemorrhage, was treated for a short time with 30 grains of mammary extract daily. The hemorrhage was reduced to a minimum, there was a corresponding increase in strength and the patient was even led to hope that she would be cured. This influence was merely temporary, the hemorrhage returning shortly after the mammary gland was stopped; but was this proof enough that the antihemorrhagic effect was due to the remedy and not to suggestion, other treatment or coincidence?

Looking at this from another angle the evidence is not so complete. The breasts are rarely removed for therapeutic purposes in women early in ovarian activity; though there seems to be some proof that this operation is not without influence upon endocrine function. We know, however, that the function of ovulation may be retarded and sometimes entirely stopped by prolonged lactation, and the writer has seen a case of premature menopause in a young woman which resulted in our opinion solely from an inordinately prolonged period of lactation—four years!

Not uncommonly we find women with large mammary development whose menses are noticeably

*Including also the article by Briggs in this issue, page 188.

scanty, though this is far from a rule. On the other hand in spayed dairy cows it is well established that the period of lactation is prolonged. It is also well known that pregnant cows as a rule show a tendency to lessen their milk producing powers soon after pregnancy takes place.

There is opportunity for some animal experimentation to demonstrate the accuracy or futility of our views that the mammae have internal secretory powers; and it should not present great difficulty to remove the mammae in a number of animals and watch the functional and histologic changes in other endocrine organs, notably the ovaries. From a clinical standpoint, too, there should be numerous experiences to substantiate this position, or not, as the case may be; and it is hoped that future issues of this journal may contain scientific evidence on this subject, since it is intimately concerned with certain phases of clinical gynecology and if the endocrine function of the mammae is proved we shall have an explanation of the clinical experiences with mammary therapy already referred to.

HENRY R. HARROWER.

# ORIGINAL COMMUNICATIONS

## RECENT VIEWS AS TO THE FUNCTION OF THE ADRENAL BODIES

By Swale Vincent, M. D., Winnipeg
(From the Department of Physiology of the University of Manitoba)

IF we hope to gain any exact information as to the diseased conditions of the adrenal bodies, the clinical disturbances which arise from such conditions, and the rational treatment of them, it is essential that we keep in mind the most recent and the most matured observations relating to the physiology of these bodies.

No attempt will be made in this place to deal with the whole subject of the functions of the adrenal bodies. The object of the present communication is to emphasize certain broad conceptions and to discuss certain fundamental topics in accordance with the results of the most recent investigations.

It is certain that in lower vertebrates the cortex and the medulla constitute representatives of two separate and independent series of organs, and there is no reason to suspect any physiological relationship between the two. In mammals a mass of chromaphil cells has become enclosed in the adrenal (or "cortex") and we have thus formed what we know as the adrenal body.*

Whether this partial coming together of the two systems in higher animals has any physiological importance we do not know. On the whole the safest

*It must be remembered, however, that even in mammals, there are outstanding portions of the original chromaphil bodies and of the original cortical bodies.

attitude is one in which the assumption is made provisionally that the two portions, cortex and medulla, have separate and independent functions. At any rate there is no good evidence of an experimental or clinical nature which warrants us in believing that the adrenal body as a whole has any definite functions. We know nothing of the functions of the adrenal body regarded as an organ on its own account.

Modern works for the guidance of practising physicians are often very confused on this point. Thus Falta (6) says: "Already at an early period some of the chromaffin cells have broken through the complex of cortical cells to form the medulla. Through the descent of the genital organs small parts of both systems are displaced. This shows that the former complete physiological independence of both systems later gives place to a common function, at least in part (Biedl), which fact is also indicated by the previously mentioned relations of the blood-vessels. It is indispensable for the comprehension of diseases of the adrenals to consider that the two systems for a great part are functionally independent. The higher we go in the classes of animals, the greater become the complexes of the two systems that finally unite to form a single organ, the adrenal."

Now the present writer begs to submit that the fact that certain masses of chromaphil cells break into the interior of the cortex does not prove that any functional relation between the two becomes established, nor does the fact that through the descent of the genital organs small parts of both systems are displaced, bear upon the point. The same may be said of the relations of the blood-vessels. But in the next sentence it is urged that "the two systems for

a great part are functionally independent." Finally the writer returns to the idea of a single organ. Surely the matter would have been clearer if the writer had merely expressed a doubt as to any possible physiological connection between the two systems.

It seems to be well established that total extirpation of both adrenal glands will invariably cause death of the animal.* The question naturally arises whether death is to be attributed to loss of the cortex, or of the medulla, or of both of these. In the work of Falta above referred to we do not find any adequate statement of our present knowledge of this subject. The author says: "The sure knowledge that the cortical system and chromaffin system are in like manner important for life was first mentioned by later investigators (I mention only Biedl and Hultgren and Andersson)† who took into consideration the presence of accessory adrenals."

Now, in the first place, there is no "sure knowledge" that the cortical system and the chromaphil tissue are in like manner essential for life. There is, in fact, every reason to believe that such is not the case. Biedl, whom Falta quotes, has urged very strongly that it is the cortex and not the medulla (or the chromaphil tissue) which is essential to life. This investigator found that rabbits and dogs would survive removal of all but one-eighth part of both adrenal bodies, provided that the portion remaining consists of cortex. (4) He found also that removal of the interrenal body of elasmobranch fishes is uniformly fatal. Many years ago the present writer (18,

*A few exceptions to this rule have been recorded, but they scarcely affect the essential validity of the thesis.

†I have made minor but essential corrections in quoting.

19) attempted to solve the problem by extirpation of the corpuscles of Stannius from the eel. But the negative results which were obtained were later fully explained by the discovery of a second cortical representative. This discovery was made by Giacomini (7) who described a mass of cortical adrenal cells in the "head kidney" of teleostean fishes.

The results obtained by Biedl were recently confirmed by Wheeler,* who carried out a series of experiments in my laboratory. An attempt was made to remove the medulla of both adrenal bodies from a number of dogs, leaving the cortex undamaged. This was not precisely achieved, but it was found that the only fatal cases† were those in which very considerable damage had been done to the cortex as well as to the medulla. In some cases the abdominal chromaphil body (Vincent, 20) was removed as well as the adrenal medulla. Of course in such experiments groups of sympathetic chromaphil cells, as well as scattered cortical "accessory" bodies must be left behind. But this fact does not seriously affect the logic of the argument that it is the cortex which is essential to life. For, since removal of both adrenals is fatal, and removal of the medulla alone is not, it follows that the cortex is the essential part of the gland so far as the maintenance of life is concerned.

After the epoch-making discovery of Schafer (15, 16) that adrenal extracts raise the blood-pressure, there was a growing tendency to assume that the function of the adrenal (or, at least, of its medullary portion) is to help to maintain the normal blood-

*Results not yet published.

†At any rate among the animals which died of adrenal insufficiency.

pressure and to keep up the tone of sympathetically innervated structures in general. The present writer was one of the first to grow suspicious on this point. If the constant secretion of adrenin into the blood-stream and its action upon the sympathetically innervated vascular muscle is an important factor in the maintenance of the normal blood-pressure, then it ought to be possible by tying or clamping the veins issuing from the glands, to keep down the blood-pressure at a low level during the period of clamping or tying, and to allow it to reach its normal level on releasing the clamp or the ligature. Some writers have claimed that they have obtained this result. But Young and Lehmann (*22*), working in my laboratory, made an attempt in dogs to dam back any secretion which the glands may pour into the blood-stream, and, after an interval, to remove the obstruction, and allow the accumulated adrenin to flow into the general circulation. A cannula was inserted into the carotid artery, the adrenal glands were exposed through an abdominal incision, and a double ligature passed beneath the organ on each side; the ligatures were tied on each side of the gland above the vein, so as to form two pedicles. The ligatures were left in place for from ten to thirty minutes, and then released, and the blood-pressure tracing continued.

Out of eight experiments, there was no effect on the blood-pressure in three; in two there was a slight rise after releasing the ligatures; in the remaining three there was a decided rise of pressure (comparable with that which follows injection of adrenin into the circulation) lasting about three minutes. In one case the effect was repeated by tightening the ligatures a second time, and then releasing them.

It is important to note that in these experiments after tightening the ligature there was very little, if any, fall of blood-pressure. In fact the experiments merely show that adrenin is poured out into the adrenal veins.

Dr. Young (23) repeated these experiments and found that even after the lapse of several hours with the blood from the adrenal bodies absolutely excluded from the circulation, there was no appreciable fall of blood-pressure. During last winter Austmann and Halliday* at my suggestion performed a series of experiments in which the adrenals were removed or whose vessels were tied off while the blood-pressure was continuously recorded for many hours. It was found that when the experiment was continued until the animal died the blood-pressure curve was not appreciably different from that obtained from an animal simply kept under ether as long as possible. These experiments appear to show conclusively that the secretion of adrenin into the circulation is not to be regarded as a factor in the maintenance of the normal blood-pressure.

But there is another argument which militates powerfully against the theory just mentioned. It was shown by Moore and Purinton (13) that very small doses of adrenin will lower the blood-pressure, not raise it, so that the amount of adrenin which is normally poured out by the adrenal veins would tend to keep the blood-pressure down rather than up.

It is difficult, indeed, in face of the foregoing consideration, to adduce any satisfactory evidence that the secretion of the chromaphil tissue is of any use

*Results not yet published.

whatever in the normal state of the animal. (Hoskins, 11.)

But the suggestion has been made that the secretion is of great service in certain emergencies. Certain experiments of Cannon and de la Paz (5) seem to show that during times of emotional stress the adrenal bodies pour into the blood sufficient adrenin to be of some service, possibly in increasing the power of sustained muscular activity. This view has received very general approval, but it would be rash to affirm that it has been firmly established. Stewart and Rogoff (17) conclude that fright has nothing to do with the results.

The experiments of Hoskins and McClure (12) taken in conjunction with others above referred to, furnish sufficient evidence to warrant us abandoning the tonus theory of adrenal secretion. But the theory is still put forward by Falta (p. 345) and is made to account for the low blood-pressure in Addison's disease.* The fact is that we have not a single physiological observation (except perhaps the effect of adrenin on the contraction of skeletal muscles†) which throws any light on the pathology of Addison's disease.

The question naturally arises, "Why is extirpation of the adrenal cortex fatal?" The answer is simply that we do not know. It is suggested by Hoskins (11) that muscular metabolism may be at fault.

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*Falta's book is so extensively used by physicians and students that it is necessary to refer to its extraordinary deficiencies in the sections that bear upon physiological questions: Thus it is pointed out (p. 273) as something significant, not to say extraordinary, that extracts of the glandular portion of the pituitary body lower the blood-pressure. The Author and the Translator seem to be unaware that extracts of all organs and tissues have a similar action. (See Vincent 21, p. 24.)

†First observed by Oliver and Schafer. (15)

Some interesting experiments were carried out many years ago by Abelous and Langlois (1, 2, 3). This was in 1892, some few years before the discovery by Oliver and Schafer that adrenal extracts raise the blood-pressure. The French authors found that intravenous or subcutaneous injection of the blood of a frog dying after adrenal extirpation into a frog recently deprived of the glands, induced rapidly developing paralysis and death. The same injection into a normal frog only gives rise to slight temporary symptoms. Their theory was that death after extirpation results from the accumulation in the blood of one or several toxic substances, and that the adrenal bodies are capable of elaborating a substance which neutralizes the toxic effects of such substances. These observations were in the main confirmed by Gourfein (8, 9, 10), but have not received much attention by recent writers. The matter has recently been investigated by Hoskins (11), who finds that the blood of dogs that have just died of adrenal deficiency is in no degree toxic when administered to frogs.

That the cortex may exert antidotal properties was suggested by Myers' (14) observation that cobra poison, after being mixed with an emulsion of the adrenal cortex, was no longer toxic. There are a few other isolated records which seem to point in the same direction, but it must be confessed that the antitoxic theory has not been substantiated.

The following is a brief summary of what, in the opinion of the present writer, represents the state of our knowledge concerning the adrenal bodies:

1. What we call the adrenal body represents the anatomical association of two elements, each one of which is derived from a separate and independent

system. The adrenal body proper or cortex is part of the "cortical" or "interrenal" system. The medulla is simply an accumulation of chromaphil cells of the same nature, histologically, chemically, and pharmacodynamically, as similar but smaller masses along the sympathetic at other levels.

2. There is no clear evidence that these two systems are functionally related to one another.

3. The adrenal medulla (as well as the "chromaphil tissue" generally) is derived from the sympathetic nervous system, and is alleged to facilitate this system's functions in certain physiological emergencies.

4. The cortex is derived from the germ epithelium and there is considerable evidence that it has important functions in connection with the development of the reproductive organs.

5. There is a considerable mass of clinical evidence that tumors of the adrenal cortex are frequently associated with sex abnormalities.*

6. Additional evidence in the same direction is furnished by the enlargement of the cortex during breeding and pregnancy.

7. It is possible that a final solution of the problem as to the relation between the adrenal gland and sex will only be arrived at when the wider problem of the relationships between the various ductless glands shall have been solved.

8. Feeding young animals with adrenal gland substance seems to stimulate the growth of the testis.

9. The cortex is the part of the gland which is essential to life. We do not know why its removal causes death, but it is possible that this is due to some defect in muscular metabolism.

*The association is frequent, though not constant.

10. The symptoms of Addison's disease are in no way explained by the accumulated results of investigations in the comparative anatomy and the experimental physiology of the adrenal bodies.

11. It is too early to attempt to diagnose clinically any syndromata due to hyper- or hypo-function of the adrenal bodies.

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## COMMENT ON PROF. VINCENT'S ARTICLE

**Prof. G. N. Stewart, Western Reserve University, Cleveland:** I have no comment to make upon Prof. Vincent's excellent summary, except perhaps to add another proof, obtained by Dr. J. M. Rogoff and myself, that the discharge of adrenin from the adrenal is not indispensable for life or health.

When one adrenal is removed (in the cat) and the nerves which are concerned in the liberation of adrenin from the other divided by Elliott's operation (Jour. Physiol., 1912, xliv, 374) the animal recovers from the operation and lives in apparently normal health, for an indefinite period. Nevertheless, it can be shown that the rate at which adrenin is given off under experimental conditions is very greatly reduced—to one-fiftieth or even one-hundredth of the normal rate. There are differences in the amount of the residual liberation in different experiments, these differences in all probability depending upon whether the secretory nerves have been more or less completely severed.*

But in all the animals the discharge is enormously reduced, and, in some, the test employed (denervated iris, and, on drawn blood, rabbit intestine and uterus segments) have yielded no evidence of any adrenin in the blood coming from the remaining adrenal. In one cat, for instance, it was found that there was no clearly detectable content of adrenin in the adrenal blood, although by the most delicate of the tests employed, a concentration of 1:400 millions could have been detected. This, it must be remembered, was under experimental conditions which have been supposed to increase the liberation through the nervous

*It must be remembered that Elliott's operation (section of all the fibres coming to the semilunar ganglion) has never been shown to be equivalent to section of all the fibres concerned in the liberation of adrenin. What he showed was that it protected the corresponding gland against reduction of the adrenin store under the influence of morphin, tetrahydronaphthylamine, etc. This, of course, would be quite compatible with the existence of some undivided secretory fibres, since the adrenin formed might balance the discharge.

mechanism. In the mixed blood of the right heart the concentration could have been at most one-hundredth of 1:400 millions, which the most enthusiastic upholder of the physiological importance of adrenin will probably consider below the threshold of any definite physiological reaction. Yet the animal was in good health.

**Prof. R. G. Hoskins, Northwestern University Medical School, Chicago:** Professor Vincent has expressed exactly my views as to the present status of the adrenal problem; but I would add that there is no reliable evidence that under normal conditions circulating blood contains any adrenin at all. It is probably significant that as the technique of investigating the problem has improved the reported dilution of the adrenin in arterial blood has constantly approached infinity. Trendelenberg, using the very delicate frog perfusion method, found that there was present in the carotid blood of normal rabbits at most no more than one part in one or two billions,—a quantity well below the threshold of vasomotor stimulation in mammals. And Trendelenberg did not wholly exclude the possibility that the infinitesimal trace of material supposed to be adrenin was actually a vasoconstrictor substance derived from traumatized blood platelets.

Much confusion has arisen from ignoring the fact that the thoracico-lumbar (sympathetic) system can itself do anything that can be accomplished by adrenin. The adrenals at most merely reinforce the effect of normal sympathetic impulses. Therefore, to ascribe promiscuously conditions of low blood pressure to adrenin deficiency as is done by various clinical writers is quite without justification. The fact that adrenin may improve such conditions no more demonstrates their adrenal etiology than does the "therapeutic test" prove that pulsus irregularis is due to a deficiency of circulating digitalis. When to this unsubstantiated conception of sympathetic control

by adrenin is confidently added a theory that the automatic system is similarly dependent upon the beneficent influence of a hypothetical "hormone x" actual absurdity has been reached.

It is even possible that the adrenin problem is commonly regarded from the wrong end. Perhaps it is not the discharge but the formation of adrenin that is the important thing! It may be formed merely by way of rendering harmless some precursor that otherwise would serve as a slow metabolic poison. The fact that adrenin is found in an external secretion from the skin of certain toads supports that idea. Possibly except in times of stress the adrenin of the chromaffin tissue is changed in situ to an inert form and then discharged. This hypothesis could be extended to fit the known facts better than does the theory that adrenin serves normally to maintain the tonus of the sympathetic nervous system.

# ON THE CRYSTALLINE COMPOUND CONTAINING IODIN WHICH OCCURS IN THE THYROID

By Edward C. Kendall, Ph.D., Rochester, Minn.

**(From the Laboratories of the Mayo Clinic)**

IT is well known that desiccated thyroid gland exerts a marked physiologic activity when administered to the normal animal and man, and that the removal of the thyroid is followed by profound changes. The extremes of thyroid disturbance are seen in the two syndromes, exophthalmic goiter and myxedema; and between these are many indefinite or borderline conditions so that thyroid disturbances present a confusing mass of evidence which is not easily classified. Clinically, the cases have been classified and a basis of diagnosis established, and much light has been thrown on the progress of the disease of exophthalmic goitre.

From clinical observations the thyroid has been supposed to have a secretion which contains a substance or substances possessing certain physiologic activity; but the acceptance of such a theory in itself erects a barrier beyond which the clinician cannot go. The only passage of that barrier is by a method which will unlock the constituents of the thyroid secretion and separate the active substances in pure form. Definite conclusions could not be arrived at as long as these substances were known only by the symptoms produced by their presence or absence.

What is the substance in the thyroid that produces toxic symptoms? What is the relation of iodin to thyroid activity? Is the iodin in the gland present in a hitherto unknown substance specific for the thyroid? What is the compound in the thyroid essential

for normal life? Does the thyroid secretion contain more than one active constituent? Can the active substance or substances be separated from the gland in pure form and retain their activity? These and many more problems can be answered only by separation in pure forms of the substances in question, and by investigation of their physiologic activity.

Attempts to isolate the active principle have resulted in two classes of preparations: (1) those secured by separation of products of protein nature without decomposition or destruction of the protein molecule, and (2) those obtained by means of hydrolysis of the protein and the subsequent separation of the decomposition products. In the first class of preparations are Oswald's thyroglobulin and iodin-free nucleoprotein. Other investigators have prepared similar proteins from the thyroid. These products, which are original protein compounds unchanged in chemical nature, still retain their activity, as shown in the treatment of symptoms of cretinism and myxedema. In the second class of preparations, Baumann's iodothyrin, containing about 9 per cent. of iodin, is the result of decomposition of the proteins with sulphuric acid. The iodothyrin so obtained is about 4 per cent. of the total weight of the dried thyroid. Other decomposition products have been obtained by Hutchinson working with pepsin and trypsin on the thyroid proteins. Hutchinson separated in this way a product containing 3.6 per cent. of iodin.

Another means of throwing light on the nature of the iodin compound has been to prepare various iodin compounds and test their physiologic activity. Di-iodotyrosin, tetra-iodohistidin, tri-iodo-imidazol,

iodized tryptophan, and iodized phenylalanin and other organic compounds have been tested in this way, but no compound has been found which produces effects similar to those of desiccated thyroid.

The object of the writer's investigations summarized here, was to isolate in pure form one or more chemical compounds which possess physiological activity. Dialysis was used as a preliminary study of the proteins of the gland and the nature of iodin combination. Desiccated thyroid, either in suspension or dissolved in dilute alkali, was found to lose less than 5 per cent. of its total iodin by dialysis in a collodion sac against running water. Experiments were then made varying the temperature and acidity of the dialysate. These results showed that increase in temperature and acidity favored dialysis of the iodin compound, and as much as 40 per cent. could be made to pass through the sac in this way. Attempts were then made to alter the nature of the proteins to see the attending influence on dialysis of the iodin. Boiling in strong sodium hydroxide allowed 80 per cent. of the iodin to pass the dialyzing sac. Boiling with sodium hydroxide and hydrogen peroxide allowed 94 per cent. to pass.

These results showed a decomposition of the protein and a probable splitting off of iodin in the inorganic form. As such vigorous treatment would undoubtedly destroy physiologic activity, further experiments were conducted to find some treatment which would break down the complex proteins into simpler products without destruction of the compounds so obtained. Alcohol was tried as a medium for the carrying out of such treatment. Alcohol saturated with hydrochloric acid gas was tried as a hy-

drolytic agent, but no satisfactory cleavage resulted from its use. Hydrolysis with sodium hydroxide in alcohol was then tried, and it was found that this method produced a cleavage different from any of the others. Seventy-five per cent. of the iodin was dialyzable, but it was easily shown that the iodin was not split off as sodium iodide, but still existed in organic combination. After it was shown that sodium hydroxide in alcohol altered the nature of the protein to a marked degree, dialysis, as a criterion of the nature of the iodin combination, was discontinued and a detailed study of the chemical properties of these products of hydrolysis was begun.

No specific precipitant was found for the iodin compound in either an alcoholic or aqueous solution. After many attempts to find such a reagent it became apparent that the iodin was present in two different forms of organic combination. About 50 per cent. of the total iodin was soluble in acid and the rest was insoluble. As the solubility in acids affected a separation between the two apparently different iodin compounds, this treatment was used as the first step in the separation of the products of hydrolysis. Those compounds insoluble in acid are designated constituents of Group A, and those soluble, constituents of Group B.

All the constituents of Group B are easily dialyzable. Saturation of a solution of B with ammonium sulphate produces a sticky, tarry precipitate which evidently consists of amino-acid complexes and carries down with it about 80 per cent. of the iodin in B, showing that it is still present in organic combination. The iodin compound in B is precipitated to a large extent with mercury sulphate, and almost quan-

titatively with silver sulphate in the presence of magnesium oxide. A large percentage of the iodin is split off by this treatment. Oxidizing agents, even copper acetate, also easily split off the iodin from its organic combination.

A more extended study of Group A showed that the most striking chemical property of A is its acidic nature. All the constituents of A are easily soluble in dilute alkali or ammonia, and are reprecipitated by any acid stronger than carbonic acid.

Experiments with organic solvents showed that uncombined sulphur, fatty acids, and about 10 per cent. of the iodin in A is soluble in ether. The fatty acids doubtless came from the fats which were saponified by the alkaline alcohol and the sulphur probably resulted from the decomposition of cystine. Further experiments showed that the solubility of the iodin compound in organic solvents varies greatly, it being least soluble in petroleum ether. The second step, therefore, for the purification of A is the removal of fatty acids and sulphur by extraction with petroleum ether. The product thus obtained contains about 4 per cent. of iodin, and this preparation may be dissolved in alkali and reprecipitated with acids without appreciable loss of its total iodin. This treatment slowly removes some constituents containing nitrogen but no iodin, so that the percentage of iodin in A may thus be increased to about 6 per cent.

This preparation is a dark brown powder insoluble in water and acids, easily soluble in dilute alkali and ammonia. Its alkaline solution is precipitated by copper hydroxide and to a large extent by barium, calcium, and magnesium salts. It is almost entirely soluble in ethyl acetate, but by partial extraction with

this solvent it is possible to separate A into two fractions. In the ethyl acetate soluble portion of A the percentage of iodin may be increased to 13 or 14 per cent., but the ethyl acetate insoluble fraction contains only 1.5 per cent. iodin.

Except for the solubility in ether the general chemical properties of A closely resemble those of a fatty acid. By further hydrolysis of the A group the compound containing iodin has been separated in pure crystalline form. Its exact formula cannot now be stated. It crystallizes in microscopic needles that melt around 220 degrees C. It is very insoluble in alcohol, ether, water, acids, and sodium carbonate. Dilute hydrochloric acid dissolves 1 part in about 200,000. It is readily soluble in dilute alkali and ammonia.

The thyroid having been separated into several different constituents, it seemed desirable to test each one for its possible physiologic activity. These preparations were first tested with normal dogs kept in metabolism cages. Administration of Group B constituents by mouth or by subcutaneous or intravenous injection produced no apparent effect on the temperature, blood-pressure, pulse rate, nitrogen balance, or weight. Administration of Group A constituents by mouth or subcutaneous injection produced the typical so-called hyperthyroid symptoms: increase in pulse rate, slight increase in temperature, marked increase in nitrogen elimination with loss of weight, increase in nervous irritability, and, later, tremor.

These results showed that the toxic symptoms following administration of the gland can be produced by a small group of constituents which amount

to only 4 or 5 per cent. by weight of the desiccated thyroid.

Further investigations concerning the injection of Group A constituents were carried out on a large number of dogs under varying conditions. A typical result is as follows: Weight of dog 10 kilos; pulse rate during previous ten days, 90; 200 mgm. of A used for each injection. Following the injection there is no immediate effect on the temperature, pulse rate, or blood-pressure, and twenty-four hours after the injection there is still no apparent change. The substance injected seems to be inert, but at this time another injection of 200 mgm. is given and the observations continued. From thirty-six to forty-eight hours after the first injection the dog appears restless, the temperature is slightly increased, and the pulse rate has reached 120. The observations and daily injections are continued. On the fourth or fifth day the dog is in a highly nervous condition, restless, with tremor, and there is generally severe diarrhea; the pulse rate is between 200 and 250. Beside the high rate, the pulse has changed its character, becoming hard and hammer-like, with spasms of tachycardia. Although the daily injections are continued at this time, the dog rapidly becomes better, the pulse rate decreases to about 120, and the hard, pounding effect disappears. If the injections are now stopped the dog returns to normal, the pulse rate even dropping to 68 to 70 in some cases.

Having shown that toxic effects are produced by a certain group of constituents of the thyroid, attempts were made to determine the chemical nature and to isolate in pure form the toxic substance contained in this group of compounds.

The presence of iodin as a normal constituent of the thyroid has been known for twenty years. During this time many controversies have arisen out of attempts to explain the relation between the physiologic activity and the presence of iodin. From the beginning of this investigation the isolation of the compound containing iodin was held as the main objective, hence the iodin content of the various preparations of the A constituents was always determined.

By the use of A made from beef, hog, sheep, and pathologic human thyroid it was readily shown that the toxicity of A is directly proportional to its iodin content. By extracting A, containing about 5 per cent. of iodin with ethyl acetate, it may be fractioned into two parts: one containing about 9 per cent. of iodin and the other 1.5 per cent.; but, taking iodin as the standard and the effect on the pulse rate as the criterion, both these preparations produced toxic effects. This indicated that the active substance in each case was the compound containing iodin, and that this substance, combined differently in the two preparations, has differing solubilities.

The toxic effects of A were first produced by preparations containing from 4 to 5 per cent. of iodin. Later the A constituents were further broken down and a purer form, containing 25 per cent. iodin, was obtained. Injection of this under the same conditions, using iodin as the standard, produced the typical effect.

Finally, the iodin-containing compound was isolated in pure crystalline form having a constant iodin content of 60 per cent. These pure white crystals used in amount equivalent to previous injections, keeping A-iodin as the standard, produced the typical

symptoms with the same severity. We can, therefore, conclude that the substance in the thyroid responsible for the production of toxic symptoms is the compound containing A-iodin, and that this compound can be separated in pure crystalline form without loss of its activity.

To determine whether the sudden improvement in the general condition following a series of injections of A resulted from the development of a tolerance to the A compound, a dog was injected until in a highly toxic condition, and was then allowed to return to normal. To a second dog two series of injections were given, the second series being precisely similar to the first. Under the effect of the second series the dog lost weight, had severe diarrhea, became nervous, and appeared to react as severely as during the first series except in regard to the pulse rate. At no time was the rate as high, and it did not develop the hard, pounding property to such a degree. The other symptoms followed much the same course as during the first series. To a third dog three series of injections were given, the previous conditions being observed. Again, the dog reacted as before, but after the third series appeared less capable of throwing off the toxic effects. While the pulse rate was not high, there were spasms of tachycardia when the rate reached 280 to 300; but when quiet and not under excitement the rate was about 150.

These and other results indicate that the A-iodin compound does not work in a rapid and direct manner, and that some form of tolerance is produced. Further experiments are being carried out to explain more fully the factors involved.

The physiologic results on dogs esatblished the

general toxicity of A and the non-toxic effect of B sufficiently to warrant the use of these preparations for therapeutic purposes in cases of thyroid disturbance, and during the past five years many patients have been treated.

As repeated injections over long periods are impracticable in man, the split products were always given by mouth. The results obtained may be briefly stated to be entirely in accord with the preliminary tests on dogs. No toxic effects have ever been produced by the B constituents, although more than 200 patients have been treated; but the A constituents, even in small amounts, produce toxic effects.

The severity of the condition following administration of A to normal individuals varies greatly, but in general it is as follows: If to a normal individual with a pulse rate of about 75 and a weight of about 75 kilos sufficient A is given per day to contain 3 mgm. of A-iodin, on the day following the first dose there is no apparent change except a slightly increased pulse rate. If the same daily dose is continued the patient slowly reacts, and in the course of eight or ten days nervous symptoms develop, the pulse rate is from 130 to 140, there is a tendency to perspire more freely on exertion, and the patient may be short of breath and easily tired. At first appetite is increased but later is lost, and nausea, and sometimes diarrhea develops. During this time the patient usually loses weight, from 1 to 5 kilos (idiosyncracy?). If smaller doses are given the severity and course of symptoms are modified, but the patient will react to very small amounts of A. If large doses are given there results a serious condition in which the above symptoms are exaggerated.

As in the tests on animals, the therapeutic results on the human being were first obtained with preparations of A containing about 4 to 5 per cent. of iodin. Later they were repeated, using the purer form of the compound that contained 25 per cent. of iodin, and, finally, the typical effects with the same severity were obtained by using the pure crystalline compound containing 60 per cent. of iodin.

These results brought out a great difference in the sensitiveness of dog and man to the toxic iodin compound. To produce effects in dogs, about 1 mgm. of A-iodin per kilogram weight of dog is required for a daily dose. In the human being severe symptoms follow the administration of as little as 1-75 to 1-25 of 1 mgm. per body weight per day. Furthermore, the nervous system seems to respond much more quickly and strongly in the human being than in the dog. Why the minimum dose required to produce toxic effects in people varies greatly is now being investigated.

In addition to observations on the pulse rate and general condition, electrocardiograms were taken of several cases. In every case a change appeared by slow and regular steps, so that a series taken on fourteen or twenty-one successive days showed a great difference between the first and last, but the change between any two days was hardly noticeable.

It has long been known that the growth of cretins is materially influenced by administration of desiccated thyroid. It was therefore interesting to determine the effects of A and B on growth and mental activity.

Case 1, a cretin, aged nine years, weight 16.8 kilos, height 93 cm., was given B alone for ten weeks. Observations on her pulse rate, weight, and height showed no appreciable change

during this period, although certain other conditions, which are discussed later, were relieved. At the end of the ten weeks a small amount of A (0.5 mgm. A-iodin) was included in the daily dose. As there was a rapid response, the pulse rate increasing to 140, the dose was reduced to 1-3 mgm. of A-iodin per day, and this amount has continued. Her weight and height were taken on the following dates:

| Dates. | Weight kilos. | Height cm. |
|---|---|---|
| January 4, 1915 | 16.30 | 92.5* |
| January 27, 1915 | 16.10 | 95.0 |
| February 27, 1915 | 16.70 | 95.0 |
| April 2, 1915 | 17.30 | 97.5 |
| May 5, 1915 | 16.90 | 97.5 |
| June 24, 1915 | 17.10 | 99.5 |
| July 8, 1915 | 18.60 | 102.0 |
| August 5, 1915 | 18.86 | 105.4 |
| September 4, 1915 | 18.86 | 106.0 |
| October 16, 1915 | 19.43 | 106.0 |
| November 13, 1915 | 20.45 | 106.7 |
| January 16, 1916 | 20.68 | 109.2 |
| February 15, 1916 | 20.0 | 109.9 |
| March 17, 1916 | 20.68 | 111.1 |
| April 16, 1916 | 19.54 | 111.1 |
| May 16, 1916 | 20.91 | 111.8 |
| June 18, 1916 | 21.36 | 112.1 |
| July 14, 1916 | 21.13 | 113.0 |
| August 16, 1916 | 21.59 | 114.9 |
| September 17, 1916 | 22.04 | 115.6 |
| December 5, 1916 | 22.95 | 116.2 |

Although no apparent effect was produced with the B constituents in respect to growth, administration of A-iodin was followed by rapid and continued increase. At the same time the mentality was markedly improved. Formerly she was phlegmatic, not easily aroused, did not play with other children, and was backward in talking. She has greatly changed in appearance, manners, and desire to play and talk.

In this case so little A-iodin was given that no toxic symptoms were produced and only a tonic effect resulted. The cretin is abnormal because of the absence of something. This deficiency can apparently be supplied by the administration of very small amounts (1-180 grain per day) of the A-iodin compound.

Another patient, case 2, similar to this one in respect to the effect on the mentality was observed with an adult suffering from myxedema. For six months this patient was treated with B alone. At the end of that time, although entirely relieved of subjective symptoms, she was still greatly troubled

*The observations on January 4, July 8, 1915, and December 5, 1916, were taken at the Mayo Clinic. The other measurements were made at the home of the patient.

with inability to keep awake. She would fall asleep in street cars, while resting on a park bench, etc., and had great difficulty in remaining awake even a few hours a day. When in this condition, small daily doses of A produced immediate and striking relief. Within a few days the patient's whole appearance changed, her naturally bright and witty personality was fully restored, and the desire for sleep was reduced to normal.

Case 3. A boy 10 years of age. Had not been treated with thyroid. Condition was typical of cretinism, dry, scaly skin, poorly nourished, distended abdomen, feeble mentality. After six months treatment with the A-iodin compound there was very marked improvement, normal skin, distention of abdomen had been relieved. There was also marked improvement in mentality. There was a rise in hemoglobin and the general condition was excellent. The daily dose for the six months was one-eighth of 1 mgm. of A-iodin.

Case 4. Young woman 20 years of age. When entering Clinic her condition was one of extreme hypothyroidism, dry, scaly skin, cold hands and feet, even in summer, great apathy and sluggish mentality. Hemoglobin 20 per cent. This patient responded very rapidly to the alpha-iodin compound and in less than three weeks showed very marked improvement. The condition of the skin was relieved, hemoglobin rose rapidly and steadily to normal, sensation of cold no longer felt in hands and feet. Mental activity was greatly increased and all evidences of edema relieved. The entire amount required to produce this change was less than one-third of 1 grain of A-iodin.

Case 5. A woman 47 years of age. During previous ten years her activities declined until she was almost in a state of helplessness. Had been diagnosed dementia praecox elsewhere and given a hopeless prognosis. Had received desiccated thyroid without effect elsewhere. Patient was extremely resistant to A-iodin, requiring enormous doses to bring about a primary change. In about three weeks the patient had reacted, the skin condition was changed to normal, mental activity was greatly increased, apathy was relieved, edema was entirely reduced, patient left Clinic so changed that her children no longer recognized her. After having reacted to the thyroid hormone her daily dose had to be reduced to 8 mgm. per seven days. If patient increases or decreases this amount unpleasant subjective symptoms follow.

The question as to whether the thyroid contains more than one physiologically active substance cannot be answered definitely at this time, but there is

evidence that at least one other substance besides the compound containing A-iodin produces physiologic effects under certain conditions. The acid-soluble group of constituents, designated B, produces no apparent effect when given to normal dog or man, but certain symptoms of myxedema and some conditions of the skin appear to be relieved by the administration of B alone. The symptoms in myxedema relieved by B alone are burning sensations of the skin, with smarting, itching areas, soreness of bones and joints, and cramps of the muscles. No stress is laid on the relief of these symptoms, but they are mentioned in the possibility of drawing attention to the condition in other cases. They are present only in the more severe types of myxedema.

Also, a dry, scaly skin with absence of perspiration in cases diagnosed myxedema is relieved by B alone. Engman has treated a number of such cases, and among them two patients suffering from dermatitis exfoliativa. In practically all cases improvement has been noted, and in no case have there been any toxic symptoms produced. At our clinic, 92 cases have been treated with B constituents, and in no case have there been any toxic effects noticed. Twelve cases of cretins and mongols have been treated over thirty days with large doses of B. Pulse rate, respiration, temperature, and weight were taken for the entire period. While there were individual variations the average results showed no apparent toxic effects.

This non-toxic effect of the B group of constituents is in strong contrast with the A group, since they both contain iodin. The iodin-containing compound in A has been isolated and its toxicity shown; the iodin in B is in organic combination, but the

nucleus to which it is attached is unknown and no relation of iodin to activity is evident. While no definite proof of the relation of the iodin compound in the B constituent compound had been isolated in pure form it seems highly probable that the iodin compounds in B are intermediate stages in the elaboration of the A compound from iodin taken with the food. The chemical identity of the iodin compound in A is established and although a pure crystalline substance, its structure is extremely complex, having a molecular weight of 586. It is theoretically impossible to pass by one operation from inorganic iodides taken in with the food to the completely elaborated A-iodin compound. Intermediate products must exist and it seems undoubted that these are found in the B group of constituents. The amount of the total iodin in the gland which may exist in the A form, that is, insoluble in acids, varies from two to three per cent. up to 40 or 50 per cent. It is highly probable that some equilibrium exists between the two forms so that in normal conditions a constant percentage of the total iodin is in the A form, the rest is retained in the gland in the physiologic inert B form. Under conditions of thyroid disturbance this relation is disturbed and in the acute stages of hyperthyroidism very little iodin is found in the gland and what there is is mostly in the B form. The percentage of the total iodin which is in the B form varies with the duration of symptoms and severity of symptoms. By the analysis of a large number of cases it is possible to follow this decrease in the total iodin as the acute symptoms develop and after the crisis has been passed it is readily shown that the iodin in the gland

increases and the percentage of the total iodin in the A form increases.

Since it has been shown to be possible to produce hyperthyroid symptoms by the administration of the A-iodin compound the small amount in the gland in the acute stages of hyperthyroidism is not to be interpreted as a cessation of the activity of the gland at this time but is more correctly interpreted as a loss of storage capacity upon the part of the gland. The production of the substance may be as great or greater than normal but it is not retained in the gland. The physiologic activity of the B group of constituents is not at all clear. It is impossible to produce toxic symptoms by administration of this portion of the thyroid and it is impossible to relieve the symptoms of myxedema, but certain indefinite skin conditions seem to be relieved by this group of substances. It is not due to the result of the activity of the iodin compound in B, because it is possible to remove this and secure the results with the iodin-free constituents.

**Conclusions.** 1. By an alkaline alcoholic hydrolysis the thyroid proteins are broken into many simpler constituents, which by their solubility in acids are separated into two groups. Those constituents insoluble in acid are designated group A and those soluble, group B. No definite crystalline compound has been isolated from group B, but it appears to be composed of mixtures of amino-acid complexes. About one-half the total iodin in the thyroid proteins appears among the group B constituents. The nucleus to which the iodin is attached is unknown.

By continued hydrolysis the group A compounds have been further separated and the iodin-containing

compound has been isolated in pure crystalline form, having a constant iodin content of 60 per cent.

2. Physiologic tests on animals and human beings have shown that no toxic effects can be produced by any of the constituents of group B. Group A constituents, however, produce the so-called hyperthyroid symptoms; increase in pulse rate, with tachycardia, increase of nitrogen elimination, with loss of weight, and increase in nervous irritability, etc. Further investigation showed that the production of these symptoms was proportional to the iodin content, that partial purification of A did not destroy the activity, and finally that the compound containing A-iodin produced these effects in all stages of purity up to and including the pure crystalline form.

3. The amount of the A-iodin compound necessary to produce symptoms is extremely small. One-half milligram (1-120 of a grain) per day produced marked effects in a cretin weighing 15 kilos. The susceptibility of animals and man to this compound varies greatly, but the human being responds much quicker and to a far greater degree than the dog. Some form of tolerance for the compound is produced. In very small doses the A-iodin compound exerts a tonic effect, and appears to be essential for normal growth and life.

4. Administration of A-iodin to man produces changes in the cardiogram.

5. Although B produces no toxic effects, it appears to possess physiological properties in certain conditions of the skin.

6. The toxic properties of A are due to the isolated iodin-containing compound; and there appears to be no relation between activity and iodin in B.

# A BRIEF HISTORY OF THE DEVELOPMENT OF OUR KNOWLEDGE OF THE DUCTLESS GLANDS*

By Gustav Baar, M. D., Portland, Ore.

FOR hundreds of years the medical world believed in the "consensus partium," which means that physicians assumed a mutual influence of the activity of the various organs of the human body upon each other. This correlation was explained on a nervous basis, the correlation being supposed to be brought about by means of the centripetal and centrifugal nerves.

The "reflex phenomenon" became known through the studies of Descartes in the 17th century, and more especially in the 19th century, when this phenomenon was more clearly elucidated by the work of the Viennese physiologist, Prochaska. Of course this neural correlation of organs was not the only hypothesis in vogue. There was also the humoral hypothesis, as represented in Hahnemann's teachings ("Homoeopathy"). This latter vindicated to every individual organ of the human body a certain influence upon the juice-mixture of the whole body. The doctrine of "isopathy" went the doctrine of homoeopathy one better, for it recommended as a therapeutic means against diseases of the various organs the use of the corresponding healthy organs: for instance, the lungs of fox for lung diseases; the liver of wolf for liver diseases; the eyes of oxen for eye diseases, etc. A replica of such procedure is found in the more modern questionable advertisements of opotherapeutic extracts.

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*Read before Portland (Ore.) City and County Medical Society March 7th, 1917.

Medicine entered a new era when Harvey in 1628 discovered the circulation: the blood now was assumed as the means of communicating between the various organs. Our confreres of those times gone by knew nothing, however, of the secretions from the various body structures, secretions which enter the blood stream by other than the known secretory ducts—though we note in Swedenborg's writings a remark that the liver and the pancreas perform a much greater chemical task than one would be led to assume from their secretory ducts; furthermore, that these organs, in conjunction with the spleen, bring about the purifying of the blood.

Then came Theophile de Bordeu, from Montpelier, claiming in 1775 that every organ creates specific bodies necessary for the integrity of the whole organism, which enter the blood either by lymphatic or venous channels. He thus explained the symptoms accompanying castration, puberty, the menopause, etc., and divined the importance of secretory anomalies as a basis for some of the pathological changes in the human body.

The first one, however, who drew a line between the "secretion" and "excretion" of the various glands was Johannes Muller in 1830. Among the secretory organs he classes the spleen, thyroid, adrenals, thymus and the placenta.

The first to prove experimentally the influence exerted by the internal secretion of a gland upon the blood mixture, and through the latter upon the whole body, was A. A. Berthold, professor in Gottingen, in 1849, who transplanted the testicles of young cockerels and noted that these cockerels, in spite of being castrated, remained normal cocks as far as vocal pow-

ers, sexual instinct, desire of combat, comb growth, etc., were concerned. Thus the existence of an internal secretion of the testicles was first accurately established.

In 1855 Claude Bernard pointed out the difference between the internal and external secretion of the liver: the latter furnishing the bile, the former producing an accumulation of glycogen within the liver and its outflow into the blood as sugar.

Shortly after this came Brown-Sequard, who taught at the medical faculty in Paris, in 1869, that all glands, whether endowed with excretory ducts or not, contributed useful and necessary substances to the blood, which, when lacking, produced pathologic symptoms. This same savant, twenty years later, set the birthdate for our knowledge of the therapeutics of the internal secretions when he, at the ripe age of 72 years, reported before a memorable meeting of the Paris Societe de Biologie, June 1st, 1889, some experiments made on his own body with subcutaneous injections of testicular juice; he claimed to have observed on himself, after such treatment, a surprising increase of physical vigor, cerebral function, appetite and intestinal activity. Since that time we have found out that the ovaries, as well as the testicles, produce "hormones" that originate in parts of the glands other than those producing the external secretions; in the male they originate in the interstitial cells of Leydig, as Hanes found in 1911; in the female probably in the corpora lutea. The functions of these sexual hormones are chiefly connected with sexual life, however they also have reciprocal relations with many other organs of internal secretion (thyroid, thymus, etc.).

In the comparatively short period which has elapsed since the epochal announcement of Brown-Sequard, a new field for research in physiology, biology, pathology and therapy has developed, an era of understanding and hope. Brown-Sequard thus impressed the medical world with a view that the glandular organs, be they with ducts, like the pancreas, liver, gonads, including also the duodenal mucosa, or without ducts, like the thyroid, parathyroid, thymus, hypophysis, or adrenals, give off to the blood certain substances that are necessary for the welfare of the body as a whole. To such substances that are derived from one organ and influence another after their passage into the bloodstream, Starling later (1902) gave the name of chemical messengers, or "hormones" from the Greek, I arouse, or set in motion.

The evidence of the existence of such hormones has been furnished in three ways:

1. Substances, physiologically active, were demonstrated in the blood or lymph leaving the gland in question; such direct and conclusive proof has been furnished as yet only for one gland, the adrenal.

2. Excision of the gland produced characteristic changes in the vital processes, which could be prevented by implantation of the gland in question or by the administration of preparations of the same gland. This sort of evidence was brought out regarding the hormones of the pancreas, thyroid, parathyroid, hypophysis, adrenals and sex glands.

3. Pathologic entities of supposed hyperfunction of some glands could be imitated artificially by administering overdoses of the substance of the gland in question. For instance, the "Graves' complex" could be produced by overfeeding with thyroid gland,

or something similar to diabetes insipidus by pituitary gland injections.

Let us take up now the history of the development of our knowledge regarding the internal secretion of the different glands. In practical importance the thyroid is undoubtedly the first.

THYROID. While Schiff was the first to attempt to combat thyroid deficiency by transplantation experiments in dogs in 1859, it remained for Reverdin and Kocher in 1882 to publish their observations on patients from whom the thyroid had been removed (cachexia strumipriva), and thus call the attention of the medical world to the importance of the gland. Within a few years it was recognized that the underlying cause of cachexia strumipriva, sporadic and endemic cretinism and myxedema (Ord in 1882 thus named the condition which Sir William Gull described five years before him), was the same in all, viz., the deficiency or absnce of the thyroid; on the other hand, hyperfunction of the thyroid gland produced Graves' disease (exophthalmic goiter), though conclusive demonstration of an excess of thyroid secretion in the blood of those patients has not been furnished. In 1915 Cannon demonstrated that hyperthyroidism may result from stimulation of the nerves leading to the thyroid gland.

PARATHYROIDS. These glands were first described by Sandstrom in 1880; it was soon found that tetany developing after thyroid operations was due to the accidental removal of the parathyroids. The syndrome accompanying parathyroidectomy is characterized by an increased irritability of the peripheral neuron, muscular tremor, convulsive seizures, particularly in the hands and feet, Trousseau's phenom-

enon (pressure on the brachial nerve causing contraction of the hand) and Chvostek's phenomenon (tapping on the facial trunk causing facial twitching). MacCallum and Voegtlin showed in 1909 that the tetany is due in part to a loss of calcium from the tissues, the injection of calcium salts relieving the symptoms, due largely to their depressing the excitability of the motor nerves. Apparently the parathyroid glands exert some influence upon the retention of calcium by the nerve tissues. A disturbed calcium metabolis has been assumed, since it occurs in diseases often associated with tetany: in rickets osteomalacia, pregnancy and lactation.

THYMUS. This gland has an important relation to the sex glands, to bone growth, and also to the thyroid. Bartel and Herman reported in 1911 that they had frequently found enlarged ovaries in the so-called status lymphaticus, a condition consisting of enlarged thymus, hypertrophied tissues elsewhere in the body, constitutional hypoplasia of the aorta and of the chromaffin tissues, which is not uncommonly responsible for sudden death. Our knowledge of the function of this gland is as yet very unsatisfactory.

HYPOPHYSIS or Pituitary Gland. In 1889 Rogowitsch noticed hypertrophy of the hypophysis after extirpation of the thyroid. In the same year Marie discovered an association between acromegaly (an entity characterized by enlarged hands and feet, thick lips, protruding lower jaw, lower incisors extending beyond the upper, increase of hair in various part of the body, enlarged sexual organs, but loss of sexual function, glycosuria) and anatomical changes in the hypophysis.

In 1895 Oliver and Schafer announced that extracts from the pituitary gland caused a rise of blood pressure when injected intravenously through their constricting effects upon the blood vessels. In 1898 Howell ascribed the origin of these substances to the posterior lobe (nervous lobe) of the hypophysis.

In 1901 Froehlich described a syndrome under the name of "dystrophia adiposo-genitalis" (obesity about the abdomen, buttocks and breasts, giving a feminine type of figure, retardation of skeletal growth, with short extremities, small hands and feet and sexual infantilism); all these symptoms are due to the hypofunction of the pituitary gland (probably of the anterior epithelial lobe secretion).

In 1907 Paulesco reported death after total extirpation of the gland, whereas partial extirpation is followed only by very characteristic effects upon growth and development. In 1909 Cushing and Homans showed the gland's relation to carbohydrate metabolism. Pituitrin is the therapeutic booty resulting from all these researches. This extract of the posterior lobe is used chiefly for its constricting effects upon non-striated muscles, especially those of the uterus, blood vessels, gastro-intestinal tract, smooth muscle in the mammary gland and bladder.

ADRENALS. Next to the thyroid gland, our knowledge of the adrenals has found most promising development. Attention was first called to the importance of the chemical influence of these glands by the classical paper of Addison, published in 1855, in which he described a disease characterized by muscular and cardiac weakness, low blood pressure, subnormal temperature, apathy, vomiting and diarrhea, bronze pigmentation of the skin and mucus mem-

branes, and a progressive cachexia leading almost always to death. The majority of these patients show a tuberculous degeneration of the adrenal glands.

In 1895 Oliver and Schafer discovered the fact that extracts of the medulla of the adrenal glands, when injected intravenously, caused a rise in blood pressure. The chemical researches of Abel, Takamine and others resulted in the isolation of epinephrin or adrenalin, a definite chemical compound. The effects of the administration of this drug are essentially the same as those which follow the stimulation of the sympathetic nerves. The output of adrenin from the adrenals is increased as a result of violent emotion, fear or anger (Cannon, 1911), bringing about functional changes in the body such as cessation of gastro-intestinal movements, broncho-dilatation, increase of blood pressure and glycosuria—symptoms which can be experimentally produced by the intravenous injection of adrenalin. Elliott (1912) demonstrated that essentially the same results could be produced by sympathetic nerve stimulation.

Eppinger and Falta proved that the thyroid has an intensifying effect upon the action of adrenin.

There are other glands, like the pineal gland, mammary gland, pancreas, which are not mentioned for lack of time, and our knowledge about their internal secretions is still comparatively meager.

As Sajous has said, "the progress of medicine has been handicapped through the non-recognition of these structures which steadily are asserting their right to be classed with major organs," and this progress will be still more handicapped if we physicians fail to inform ourselves of the true progress in the science of endocrinology.

## A METHOD OF CONTROLLING HYPERTHYROIDISM

By Leigh F. Watson, M. D., Chicago, Ill.

ABOUT four years ago I observed the effect of a concentrated solution of quinine and urea which was injected into an angioma of the tongue, that had been repeatedly cauterized with carbon dioxide snow without reducing its size or vascularity. Injections of a 50 per cent. solution caused the tumor to disappear completely; the tongue assumed its normal size and color and there has been no return of the condition since.

Shortly after treating the angioma, I used the quinine and urea injection in a severe case of toxic exophthalmic goiter. The patient was too ill to stand even the slight operation involved in ligating the superior thyroid arteries; the improvement following the injection was more decided than I have ever seen following ligation. Since my preliminary report, I have used quinine and urea injections in over one hundred cases of goiter with no unpleasant effects.

I recommend the method only to relieve hyperthyroidism and not to remove the goiter. It is often true that in small toxic and atoxic goiter, the inflammatory reaction following the injection is sufficient to cause the disappearance of the tumor; but the process is slow, usually covering several months, and when used for this purpose alone, the results are liable to be disappointing.

The injection must be employed with discretion; I have used it four years, the length of time being too short and the number of cases too limited, to draw

conclusions. It is suitable for use only in a hospital by men skilled in goiter work.

Too often toxic goiter is regarded as a disease of the thyroid gland alone, while in reality all the glands of internal secretion are more or less involved. For instance, I have found glycosuria in 85 per cent. of severe cases of hyperthyroidism.

Rautmann, who has recently reported the findings from autopsies on patients dying of exophthalmic goiter, states that an enlarged thymus very frequently accompanies hyperthyroidism; the adrenals and ovaries are involved in a majority of cases; the hypophysis, parathyroids, and islands of Langerhans are less frequently affected. He states further, that the changes in the thyroid, parathyroids, thymus, and hypophysis are of a hypertrophic hyperplastic nature, while the changes observed in the adrenals, ovaries, and islands of Langerhans are of a pronounced atrophic hypoplastic type.

Barker believes that a focus of irritation or infection is often present in some part of the body aggravating the hyperthyroidism; the most common conditions associated with exophthalmic goiter are chronic tonsillitis, sinusitis, nasal polyps, chronic appendicitis, pulmonary tuberculosis, gall-stones, urogenital lesions, pyorrhea alveolaris. The association of thyroid disorder and uterine disease is often observed, and has been variously estimated as representing from fifteen to twenty-five per cent. of all cases. It is not uncommon for these patients to observe that their hyperthyroidism is worse when the pelvic lesions are aggravated.

Hertzler states that the physiologic relationship between thyroid and pelvic organs suggests that the

latter are particularly liable to be the source of irritation in producing or continuing the symptoms of hyperthyroidism. Relief of the pelvic lesion is occasionally followed by subsidence of the hyperthyroidism, and vice versa. Halsted maintains that the most puzzling cases of exophthalmic goiter are explained by the discovery of the influence of the thymus. The association of the thymus should be thought of in all cases of goiter presenting marked tachycardia and psychoneurotic disturbances with lymphocytosis. Thymus involvement is probable in cases presenting dyspnea, diarrhea, and slight enlargement of the thyroid with exophthalmos and tachycardia absent.

From time to time in the course of this study it has been necessary to conduct a series of experiments. The dog's thyroid was selected because of its freedom from pathological changes.

The thyroids of several dogs were injected with different percentages of quinine and urea solution and removed at varying intervals to show the changes that take place in the normal thyroid after injection. All injections were made under ether anesthesia and the strictest aseptic technic was observed in every case. The findings may be summarized:

The injection of weak quinine and urea solution has little effect. In three or four weeks the glands are practically normal in appearance, the destruction of thyroid cells and colloid always occurring after the concentrated solutions are injected.

The injection of concentrated solutions of quinine and urea into muscle produces an intense inflammatory reaction, resulting in the muscle being completely replaced by connective tissue.

From a study of two human toxic goiters removed

for cosmetic reasons after injection, the following conclusions may be drawn:

1. In each of these cases there was a noticeable absence of adhesions around the gland; the operation was not made more difficult because of the previous treatment.

2. It is more difficult than one might suppose, to destroy a sufficient amount of thyroid to relieve hyperthyroidism, merely by making several injections through the skin.

3. The weak solutions of quinine and urea injected into thyroid tissue are productive of only a temporary fibrinous exudate, which is rapidly absorbed with more or less accompanying hyperemia. The reaction following the strong injection is more intense and results in extensive inflammation with round cell infiltration, connective tissue proliferation and necrosis of the thyroid cells with a loss of staining properties of colloid and thyroid.

I have noticed that a number of small injections of quinine and urea produce more necrosis than a single massive infiltration.

The diagnosis of hyperthyroidism is difficult at times, especially when there is no exophthalmos or decided enlargement of the thyroid. These symptoms are of little importance and may be absent in the very severe cases that have a sudden onset. Exophthalmos is present only in a small per cent. of the cases of moderate hyperthyroidism, and not demonstrable in every case of severe toxic goiter. When exophthalmos and thyroid enlargement are absent, the heart and nervous symptoms are often treated without recognizing the underlying cause of the disease. The first symptoms noticed may be slight insomnia,

nervousness, accelerated heart action or increased exertion. Often the onset can be traced to an accident, sudden fright, parturition, grief, or great emotional strain.

Too frequently the hyperthyroid patient is not regarded as a sick person. Because her symptoms may not be severe enough to compel her to stay in bed, the physician is liable to be lax in insisting on close medical supervision. Surgeons and internists agree that any procedure for the treatment of hyperthyroidism must be based upon a period of rest, with medical, dietetic and hygienic measures suited to the needs of the individuals.

The hyperthyroid patient will usually do best away from home, removed entirely from surroundings suggesting mental and physical exertion. Inquiry will frequently disclose some particular factor of work or worry that has contributed to the symptoms or perhaps caused the disease, and which should be corrected as far as possible. Sympathetic friends and relatives should be excluded, thus giving the patient an opportunity for repose, as complete as can be, in a cheerful atmosphere.

**Organotherapy.** Organotherapy has an established place in the treatment of hyperthyroidism. It is necessary to make a careful study and examination of each patient to determine which ductless glands are contributing to the symptoms, and if their action is one of hypofunction or hyperfunction. If the condition is found to be one of decreased function, glandular extracts should be administered; if it is a disturbance of hypersecretion, a nucleoprotein serum may be given in selected cases.

**Hygienic.** A patient suffering from severe hyper-

thyroidism should have a rest of several months, on an open veranda, or in a bright, cheerful room, carefully isolated from seriously ill or noisy patients. For the first few weeks he must lie down the whole or greater part of the day. The more favorable the climatic conditions, the better for him.

**Dietetic.** Body weight can be increased best by a simple nourishing diet, with plenty of carbohydrates, milk, fats, vegetables, and a little meat.

**Medicinal.** The administration of drugs is usually not necessary and should be avoided as far as possible. The treatment of symptoms as they arise is the best rule rather than any routine medication. It is not my purpose to condemn the operation for goiter. Anyone with experience in the disease can not doubt its value as a therapeutic procedure, and in many cases it is the only treatment from which the patient may derive benefit. It is my opinion, however, that only in exceptional cases should it be the first step taken to effect a cure.

**Quinine and Urea Injections.** In selected cases, I believe hyperthyroidism can be relieved by means of injections of concentrated solutions of quinine and urea into the thyroid.

A study of thyroids removed after infiltration has demonstrated the difficulty of destroying even a small portion of the gland by injections through the skin. As one becomes experienced in the technic, it is possible to give each injection into tissue that has not been previously infiltrated; thus destroying the greatest amount of thyroid with the smallest number of injections.

For the injection I use an all glass syringe of 1 or 2 mil. capacity, fitted with a slip needle so that the

syringe can be readily attached and detached without traumatizing the thyroid. I prefer a fine platinum needle 1½ inches long.

After the usual aseptic precautions, the site of the injection is anesthetized with a 0.1 per cent. cocaine or 0.25 per cent. novocaine solution infiltrated into the skin, subcutaneous tissues and muscles, down to the gland. The syringe is now detached and the needle is thrust carefully into the body of the goiter. After ascertaining that there is no fluid in the thyroid and that no blood or air comes through the needle, the syringe is attached and the infiltration slowly made.

In cases of hyperthyroidism, I usually give from 1 to 4 mils. of a from 30 to 50 per cent. quinine and urea solution at a treatment, repeating the injections about every third day, depending on the progress of the patient. Eight to fifteen infiltrations are usually necessary to produce a marked improvement in the general symptoms and the disappearance of the bruit over the superior thyroid arteries.

The method is recommended only to relieve hyperthyroidism and not to remove the goiter. It is sometimes true that in small toxic and atoxic goiters the inflammatory reaction following the injection is sufficient to cause the disappearance of the tumor; but the process is slow, and when the injection is used for this purpose alone, the results are liable to be disappointing.

The procedure is one that is surrounded by certain dangers, immediate and remote. One inexperienced is liable to puncture the trachea or one of the large bloodvessels, or to make the injection into the soft tissues of the neck. Injections that are too ex-

tensive will produce the same symptoms of myxedema that follow the removal of too much thyroid by operation. For this reason, it is necessary to discontinue injections before symptomatic relief is secured.

The necessity of minimizing the slight pain from any injection by the use of local anesthesia can not be too strongly emphasized.

Preliminary injections into the thyroid gland of a few minims of a sterile salt solution, followed by injections of sterile water, are necessary to raise the patient's threshold of stimuli, thereby preventing an acute attack of hyperthyroidism which might otherwise follow the slight pain of the first quinine and urea infiltration. As soon as no hyperthyroid reaction follows the water injections, their usefulness is at an end. The use of quinine and urea injections without this preliminary precaution is likely to be disappointing if it is not disastrous.

The above treatment is suggested only to relieve the symptoms of hyperthyroidism and is not recommended as a means of removing the tumor in simple goiter.

Much depends on a proper selection of cases; the necessity of preventing pain from any injection, by the use of local anesthesia, is of vital importance, if acute attacks of hyperthyroidism are to be prevented, preliminary injections of sterile salt solution, followed by sterile water, will be found valuable.

The method is suitable for use only in a hospital by men experienced in the difficulties of thyroid surgery. The danger of destroying too much of the gland must always be borne in mind.

I believe the greatest field of usefulness for the

injection method which I have advocated will be found in those cases of beginning hyperthyroidism not severe enough to justify operative treatment, and as a preparatory measure to partial thyroidectomy in chronic cases of toxic goiter in which the patient is too ill to warrant any form of immediate operative procedure.

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COMMENT ON DR. L. F. WATSON'S ARTICLE

**Dr. Harry G. Sloan, Cleveland, Ohio:** We have been impressed with the value of quinine and urea injected in a concentrated solution into the thyroids of patients who show toxic goiter symptoms.

We use this solution as the mildest of all methods for diminishing the amount of secreting gland substance in the very gravely ill patients. I think as a rule these are found in the acute exophthalmic goiter, in children and at the time of puberty, it being a well recognized fact that this type of patient stands opera-

tion least well. We have found that in regard to age, patients in the third decade of life stand operations for acute exophthalmic goiter better than at either extreme of life, i. e., in the young and the very old. This fact corresponds to the ability of patients in general to withstand either hemorrhage or infection because in middle life the natural reserve of the central nervous system is more markedly developed.

Quinine and urea injections seem to give better results in the severely ill cases than hot water from the fact that the absorption of necrotic tissue caused by the injection is more slow in the case of quinine and urea than with hot water. The broken down tissue caused by hot water injections is more rapidly absorbed and undoubtedly gives rise to greater toxic action.

We graduate our dosage of quinine and urea, using 25 per cent. solution in quantities of from 1 to 5 mils.

The injection is made without general anesthesia, the skin and deep structures being perfectly blocked by novocain 1-400. In the severe cases from five to ten injections are necessary with varying periods between injections of from one week to three days.

At this stage they are able to bear ligation of the superior thyroid artery. Following this the opposite superior artery is ligated. We do not consider that these people are in a state to recover from the disease until four-fifths of the thyroid has been removed by operation and even then they must carefully observe a prolonged period of mental and physical rest of from one to two years.

# A THEORY AS TO THE CAUSATION OF UTERINE FIBROMYOMATA, WITH SOMF REMARKS ON THEIR PREVENTION AND CONSERVATIVE TREATMENT

By W. A. Briggs, M. D., Sacramento, Cal.

UTERINE fibromyomata occur in more than 50 per cent. of women between the ages of 40 and 60. This is a frequency greatly in excess of that of tumors homologous to any other tissue of the human body. The comparative size of these growths is commensurate with their frequency. The causes of the exaggerated size and frequency of these tumors, as compared with similar tumors elsewhere, must be inherent either in this organ itself, in some external organ, function or condition exercising on it a very powerful influence or in a combination of these.

From a histological standpoint, besides dilated lymphatics and blood-vessels, uterine fibromyomata consist essentially of pathologic reproductions of the normal uterine tissues chiefly muscular, fibrous and glandular, often seen to be in process of undergoing various forms of degeneration. The tumors inherit not only the structure of the parent organ but its characteristics also—a unique capacity for great and rapid development and an even more rapid involution. This explains, perhaps, their potential size but not their actual frequency.

That the causes, at least the exciting causes, of these growths, are not resident solely or even chiefly in the structure of the uterus itself is further indicated by the extreme frequency with which fibromyomata originate during the reproductive period and the extreme rarity with which they originate either before or after—a rarity approaching if not equal-

ling that of fibroids elsewhere in the human body, a rarity so great that until recently their existence had escaped the attention, personal as well as statistical, of more than one reputed authority.

The exciting causes of uterine fibroids, so frequently originating during the reproductive period and so rarely before or after this period, therefore, must be sought elsewhere than in the structure of the uterus itself. May they not be connected with the physiologic uterine hyperemia of menstruation, often pathologic in degree, frequency and duration; in the absence of the physiologic suspension of this hyperemia of pregnancy and its physiologic antagonism by mammary activity during lactation and in the pathologic congestion due to metric and parametric infections, uterine retrodisplacements, pelvic adhesions, colonic stasis and the universal corset?

That these causes may be so found is suggested by the following generally accepted facts: Uterine fibroids generally cease growing and are often partially or completely absorbed (a) after the menopause (b) during pregnancy (c) during lactation (d) after X-ray inhibition of ovarian function and (e) under the ovarian inhibitory influence of mammary extract: the uterus itself atrophies (f) during lactation and (g) during periods of ovarian quiescence and the entire female reproductive system normally atrophies after the menopause: in uterine fibrosis, ovarian activity, as manifested by profuse or prolonged menstruation, is so frequent as to be generally considered (h) its first and most important symptom and as often (i) maintained beyond, not rarely far beyond, the normal period: (j) uterine fibroids develop more often in women whose ovarian function is not normally interrupted by pregnancy and lactation.

In short all of the conditions, whether ovarian or otherwise, which antagonize, moderate, suspend or destroy the uterine function of the ovaries, either delay the growth or promote the absorption of uterine fibromyomata. If, then, as we have long known, these conditions produce atrophy of the uterus itself, why should they not also produce the same effect upon these adventitious growths within it which depend for their sustenance on the same sources both nervous, nutritive and hormonic?

From this array of facts the conclusion would seem inevitable that the exciting cause of uterine fibrosis, whether focal or diffuse, is in some way dependent on the functional activity of the ovaries.

In what does this influence consist? Hyperemia is the essential uterine expression of the periodic ovarian function. Normally it precedes the menstrual flow by several days, continues during the flow and then rapidly subsides. The uterus is thus more or less, often acutely, hyperemic for a third, not rarely even a half of the reproductive period of the sterile woman's life. In the normal married woman pregnancy and lactation suspend this recurring hyperemia for varying periods but, in our artificial modern life, with growing infrequency. Moreover the function of the ovaries like that of other endocrine glands is subject to depression and exaltation—in otherwise healthy women more often the latter as manifested by too freqeunt, profuse or prolonged menstruation, by abortive intermediate menstruation—the so-called "mittelschmerz" of the Germans—and occasionally by a seemingly continuous uterine hyperemia. When we add to this physiologic hyperemia, often present in a pathologic degree, the purely pathologic pelvic congestion due to acute and to chronic metric and

parametric infections, to pelvic adhesions, to uterine retrodisplacements, to colonic stasis and the modern corset, we have a sum-total of uterine hyperemia and congestion commensurate with the size and frequency of uterine fibromyomata.

Does not this conception of the causation of uterine fibromyomata lend itself to a rational and practical prophylaxis? Whether or not we have here traced the true pathogenesis of uterine fibromyomata certain it is that functional activity of the ovaries is a sine qua non not only of menstruation but also of the origin, and generally the growth, of these tumors. The control or regulation of ovarian function, then, as it relates to the uterus, would seem to be the first step in such prophylaxis.

Fortunately in the mammary gland, we have a powerful physiologic remedy which either antagonizes or neutralizes the ovarian hormone or inhibits its production or possibly acts more directly on the uterine circulation and nutrition. Whatever its mode of action it seems to be by far our most effective remedy in controlling or regulating excessive or perverted ovarian function as shown by menorrhagia in its various forms. Since it was proposed for this purpose by Robert Bell, of Glasgow, in 1896 a sufficient amount of clinical and experimental work has been reported to demonstrate its value beyond question. It would be impossible directly to establish the prophylactic power of mammary extract except by the careful observation of a considerable number of cases for a long period, but we may reasonably infer that it has some such action from the fact that, in a large majority of cases receiving mammary extract, menorrhagia is effectively controlled and under its

continued use large uterine fibroids often disappear even during the early reproductive period.

It should be the duty of the family physician, therefore, to correct disturbances of ovarian function as expressed by frequent, profuse, prolonged or intermediate menstruation.

Illustrating some of the results that may be accomplished in such conditions the following cases may be cited:

Case 1. Miss R., 26 years of age, otherwise in good health, complains of pelvic pain with slight vaginal discharge tinged with blood, coming on regularly nine or ten days after the cessation of normal menstruation—a typical but rather severe "mittelschmerz." No pelvic abnormity was discoverable. Mammary extract (gr. x, q. i. d.) was prescribed Feb. 2, 1916, and continued until June 10, 1916, when patient reported complete relief, continuing to the present date of both intermenstrual pain and discharge.

Case 2. Miss B., 43 years of age. Her menstruation, previously normal, has, for the past fifteen months, been nearly continuous—rarely ceasing for more than four or five days before the following period; uterus double normal size but no definite fibroid could be made out. Mammary extract (gr. xv, q. i. d.) was ordered March 5, 1916, and continued until Sept. 3, 1916, when patient reported that menorrhagia had been gradually relieved and that the last two periods had been normal in time, but scant in quantity.

Case 3. Mrs. A., 32 years of age. Severe menorrhagia; has been curetted three times with only temporary relief; had asserted that a double oophorectomy was performed five years ago for cystic ovaries, with no relief of the menorrhagia. March 20, 1916, mammary extract (grs. x, q. i. d.). Sept. 15, 1916, menstruation regular, but scant since May 12, 1916.

Besides the correction of excessive ovarian function and the consequent excessive uterine hyperemia in the manner suggested, all causes of pelvic congestion whether mechanical or infectious should be in as far as possible removed.

From a therapeutic point of view uterine fibromyomata may be divided into three distinct categories:

1. Those cases clinically suggestive of malignant degeneration either primary or secondary, of cystic or purulent degeneration, necrobiosis, pyosalpynx, parasitism, incarceration, torsion or other serious pelvic complication. These, if operable, are unconditionally surgical.

2. Cases after the 38th or 40th year free from serious suspicion of complications of the first group and yet presenting symptoms requiring prompt and energetic treatment—cases, for instance, with menorrhagia impairing the patient's health or of large tumors producing pressure symptoms, etc. These individuals should be given vigorous treatment from the outset, and in such cases I prefer mammary extract 1 gm. four times a day, ergot extract 0.2 gm. and hydrastis extract 0.1 gm. three times a day, and irradiation of the ovaries every three weeks. The following experiences are illustrative:

Case 4. Miss C., 48 years of age. Seen June 30, 1915; profuse and prolonged menorrhagia, marked pallor, dyspnea, hemoglobin 27 per cent., uterine fibroid 3½ by 5 inches. Treatment included irradiation of ovaries, mammary extract, hydrastis and ergot.

Nov. 29, 1915. Amenorrhea since Sept. 25, 1915, hemoglobin 76 per cent.

Sept. 29, 1916. Continued amenorrhea, tumor 1 by 2 inches.

Case 5. Mrs. C., 53 years of age. Seen Oct. 1, 1915; profuse menorrhagia, with an intramural fibroid, about 3 by 4 inches. Irradiation of ovaries, mammary ertract, hydrastis and ergot.

January 9, 1917, tumor gone; no flow since Nov. 10, 1916.

Case 6. Mrs. B., 42 years of age. Menorrhagia, pelvic pain, uterus three times normal size, indurated, endocervicitis, cervical abrasion.

April 28, 1916, irradiation of ovaries, mammary extract, hydrastis and ergot.

Dec. 10, 1916, amenorrhea since July 31, 1916, uterus atrophic.

Case 7. Miss P., 48 years of age. Menorrhagia, uterus retroverted, twice normal size, distinctly nodular.

Nov. 3, 1915, irradiation of ovaries, mammary extract, hydrastis and ergot.

Aug. 31, 1916, amenorrhea since Dec. 31, 1915.

Case 8. Mrs. D., 48 years of age. On Aug. 15, 1915, she reports menorrhagia of several months duration, weakness, precordial pain radiating down left arm on exertion, vertigo, hemoglobin 24 per cent., uterine fibroid, 5 by 8 inches. Treatment consisted of iron, ergot, hydrastis, mammary extract and irradiation of ovaries.

Dec. 10, 1915, Hgb. 50 per cent.; amenorrhea since Oct. 29, 1915.

March 10, 1916, Hgb. 80 per cent., uterus 2 by 3½ inches; "hot flashes" annoying; stopped mammary extract and prescribed corpus luteum extract with good effect.

July 13, 1916. Uterus atrophic; continued amenorrhea.

3. Cases free from the clinical suggestions of Group 1 and the urgent symptoms of Group 2. These cases should be treated vigorously and persistently with mammary extract, hydrastis and ergot, but, in women under 38 or 40 years, irradiation of the ovaries should not be used until either symptoms of Group 2 develop or the futility of exclusively medical treatment has been demonstrated: for effective irradiation not only sterilizes the patient but also, under the age of 38 or 40, requires very large doses of the X-ray, whose remote and possibly injurious by-effects are as yet undetermined. Until these remote by-effects are revealed by time I must distrust such treatment and particularly the enormous doses advised by Gauss in his "Intensivbestrahlung"—in one reported case (No. 196) reaching in the course of three months and twelve days, the truly "kolossal" quantity of 2284 x, or no less than 228 erythema doses! A further history of these cases might be both interesting and instructive.

In addition to 25 cases of uterine fibroids treated exclusively by mammary extract, hydrastis and ergot and previously reported I have recently found an

other case whose record had been mislaid. The history is as follows:

Case 9. Feb. 12, 1907, Mrs. M., 38 years of age, menorrhagia, sterility, pelvic distress; uterine fibroid, intramural, 3 by 5 inches; mammary extract, hydrastis and ergot. May 15, 1907, menorrhagia relieved, tumor unchanged. March 7, 1909, tumor gone, patient pregnant three months. On Sept. 27, 1909, she was delivered of a vigorous male child living now, March, 1917, at the age of seven years.

Of these 26 cases 4 did not report at all; 1 reported but once, at the end of four months; 3 elected hysterectomy—1 at the end of three months because of pregnancy, 1 at the end of three months and 1 at the end of ten months, because impatient with treatment. The remaining cases, 17 in number, ranging between the ages of 26 and 56, recovered completely and three of them have since borne children—three now living at the respective ages of 7, 9 and 12 and 1 still-born one month after spontaneous rupture of the membranes.

Assuming that the child-bearing period ends, on the average, at forty-five, in these seventeen cases something more than 80 years of reproductive life have been saved by conservative treatment. In comparison with the results of surgery this record is certainly striking enough and yet it might well have been very much more remarkable had these cases been taken in their incipiency or, still better, in the pre-fibroid stage as suggested previously.

It might seem, therefore, to be the duty of the family physician to urge on his female patients the necessity of a yearly examination for the early diagnosis of uterine fibroids as well as those conditions which predispose to them.

**Conclusions:** 1. Fibromyomata of the uterus are pathologic reproductions of normal uterine tissues.

2. Their capacity for rapid development and involution are inherited from the parent organ.

3. Their exciting cause is believed to be uterine hyperemia of ovarian origin often abnormal in degree, frequency or duration especially when accentuated by uterine congestion of infectious or mechanical origin and when not periodically suspended by pregnancy and antagonized by lactation.

4. Their development may probably be prevented by a normal reproductive life and the removal or prevention of excessive uterine hyperemia and congestion.

5. Before serious symptoms, degenerations or complications develop, they generally may be dissipated by mammary extract, hydrastis and ergot.

6. The preventive and early conservative treatment of uterine fibromyomata here outlined would prevent most if not all of their invalidism and mortality whether the result of complications, degenerations or surgical intervention and preserve or restore, in the aggregate, a by no means negligible period of potential motherhood.

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COMMENT ON DR. BRIGGS' ARTICLE

**Dr. Emil Novak, Baltimore, Md.:** With all due respect to the author of this interesting paper, it seems to me that what is true in it is not new, and what is new is certainly not proved. It is unfortunate that the title does not suggest that the paper is based upon a still unproved hypothesis as to the causation of uterine fibroids. Certainly no scientific proof has been brought forward by the author or, so far as I am aware, by any one else to justify the bold conclusion that "the exciting cause (of uterine fibroids) is uterine hyperemia of ovarian origin, often abnormal in degree, frequency or duration, especially when

accelerated by uterine congestion of infectious or mechanical origin and when not periodicaily suspended by pregnancy and antagonized by lactation."

The array of facts—(a) to (j)—set forth in substantiation of the author's hypothesis is far from convincing. For example, I fancy that few gynecologists would subscribe to the statement that "uterine fibroids are often partially or completely absorbed after the menopause or during pregnancy or lactation." How much less objectionable it would have been to conclude that "uterine hyperemia of ovarian origin" is perhaps a predisposing rather than the exciting cause of uterine fibroids.

Dr. Briggs displays a remarkable faith in the efficacy of mammary extract, which he includes among the factors which often cause partial or complete absorption of fibroids. "In the large majority of cases mammary extract effectively controls menorrhagia and under its continued use large uterine fibroids often disappear even during the early reproductive period." I am frank to say that I have never employed this therapeutic agent for such purposes, but I am reasonably sure that it has been similarly neglected by the overwhelming majority of gynecologists, and that this neglect is based upon a more or less well founded skepticism as to its therapeutic virtues.

I trust that these remarks will not be construed as superciliously critical of all medical papers which are not securely based on solid scientific facts. There can be no objection—indeed, there are many advantages—in weaving hypotheses, so long as we recognize them as such, and utilize them as a mere groundwork in our search for truth.

To sum up my personal impression of Dr. Briggs' paper, it seems to me that he has done well to call attention to the influence on the growth of fibroids of the periodic physiological hyperemia of menstruation, but I do not believe he has made out a case for his hypothesis that such hyperemia is the exciting

cause of uterine fibroids, or for his enthusiastic belief in the efficacy of mammary extract in the treatment of these growths.

**Dr. S. W. Bandler, New York City:** The author favors the idea that hyperemia is in some manner responsible for the development of uterine fibroids. This hyperemia among other causes is supposedly due to certain changes in the chemical function of the ovaries.

Since the ovaries exert such a trophic influence on the uterus and the other general structures, it is not without reason that some involvement of them, not alone from the standpoint of hyperemia, but from a trophic standpoint, may be in a great measure responsible for uterine fibroids. Here, especially, where perverted ovarian function is a responsible factor, mammary extract seems to be the natural drug for prophylactic purposes. Mammary extract controls the bleeding from the uterus in many cases, and since its relation to the ovary is undoubted, it is quite possible that by the use of the therapy and by diminution of the hyperemia, not alone the fibroid will develop less readily, but in all probability a retrogressive action is exerted.

Acting on this theory, the writer has conservatively treated a large number of cases associated with menorrhagia and metrorrhagia by the use of mammary extract, ergot and hydrastis and in some cases by the use of irradiation of the ovaries. The results are certainly most excelelnt and have in a great measure done away with a surgical treatment of these cases.

The idea of the paper is an excellent one and the result speaks for the logic contained therein. It is certainly worthy of trial, harms the patient in no wise, and if it succeeds in many instances in avoiding surgical interference, it is well worth the attention of the medical profession.

**Dr. J. W. James, Sacramento, Cal.:** The ovarian theory of the causation of uterine fibroids, although

lacking in positive scientific proof, is supported by an array of clinical findings which certainly countenance the belief that, if ovarian activity is not the exciting cause of uterine fibroids it has at least a great deal to do with their stimulation and growth. Very suggestive, if not quite convincing, are the facts that uterine fibroids develop chiefly if not entirely during the period of ovarian activity and that they decrease in size when ovarian activity lessens under the use of mammary extract and disappear, in some cases at least, after ovarian activity ceases either on account of the normal or artificial menopause or after ovarian radio-therapy.

Coincidence or a "lucky series" can hardly account for the reported success of the treatment outlined by Dr. Briggs in so many cases of uterine fibroids in different hands.

Experience is more convincing than argument and I therefore submit as evidence several cases which have occurred in my own practice:*

Miss K., single, age 36. Severe menorrhagia at irregular intervals for about one year; patient tubercular; uterus enlarged; three fibroid masses about size of fist. Mammary extract and ergotin were administered for nearly four months, at the end of which the patient had ceased to flow and the fibrous masses were greatly decreased in size. The patient died from the tuberculosis about one year after beginning treatment. The menorrhagia, however, was fully under control.

Mrs. D., age 46. Married, no children. Severe menorrhagia until patient had become extremely pale, hemoglobin 30 per cent. (Sahli). Uterus enlarged with a small fibroid in left fundus. Consultation advised hysterectomy. (Curettage and packing the uterus with astringents were of no avail.) Mammary extract was given for 6 months, also 10 X-ray treatments were given.

Patient has ceased flowing and has not flowed for 10 months; the uterus is very small and soft. Hemoglobin 75 per cent.

Mrs. N., age 36. Came for help for a very persistent constipation—a large fibroid the size of an orange was discovered to be pressing against the rectum and causing partial

*Doctor James also submitted outlines of seven additional cases treated successfully by colleagues.

obstruction. Three months' treatment as outlined (mammary extract with ergotin and hydrastis) has greatly reduced the size of the growth, which is now much softer; and at the same time the constipation is greatly relieved.

The above cases make the conclusion very definite in my mind that there is a relationship between the shrinking and disappearance of uterine fibroids and the administration of mammary extract, so much so that, though still inclined to operate in suitable cases, nevertheless, I would not condemn the patient to invalidism in case she refused operation, until I had first given the medical treatment suggested by Dr. Briggs a thorough trial.

# A CASE OF ADDISON'S DISEASE WITH MENTAL SYMPTOMS

By Beverly R. Tucker, M. D., Richmond, Va.

THE patient, a boy 19 years of age, entered the Memorial Mospital under the service of Doctors McGuire and Peple. He was tall, thin and ill-looking, and had been doing farm work. No surgical condition could be found.

The present trouble began about fourteen months ago. His family history revealed that his father was normal but that his mother died of abscess of the breast and had a nervous temperament, and that her people were also nervous. He has one brother that is frail, possibly tuberculous.

Examination on admission showed his nourishment was poor, he had lost twenty-five pounds in flesh and he was very weak. Perspiration was scant. He complained of vague subjective pains and sensations, none of which were typical of any particular thing. His reflexes were negative, except that the deep reflexes were somewhat diminished. There was no hand tremor and his pupillary reactions to light seemed sluggish.

The results of the mental examination were very interesting and showed hypochondriacal ideas, considerable emotionality, insomnia and a history of impulsive desires to get up and run. The latter seemed to be a relief reaction and overcame a certain amount of nervousness. We could get no evidence of convulsion or unconsciousness. Since he has been in the Memorial Hospital we have observed that his temperature has been sub-normal, running between 96 and 97 degrees; his pulse has been slow, averaging between 50 and 60 beats per minute, and his respira-

tion has been slow, averaging between 12 and 16 per minute. His blood pressure has been low, varying from 85 to 110 mm. systolic and from 30 to 60 mm. diastolic. His urine showed a trace of albumin, but otherwise was negative.

An examination of his blood showed the hemoglobin 80 per cent., leucocyte count from 10,600 to 10,800, red cells from 5,280,000 to 5,824,000. A gastric analysis was attempted but he was unable to retain a test meal at the time. His feces have been examined three times and have always been negative, except that once a trace of blood was found. There were two blood Wassermann reactions and one spinal fluid Wassermann made, all of which were negative. His spinal fluid was also negative as far as the cell count and globulin content were concerned.

Examination reveals no axillary hair and very scant pubic hair. There is no glandular enlargement except a slight enlargement of the epitrochlear glands. His skin is dry and vasomotor mottling is observed about the lower extremities, and distinct bronzing can be seen on the face, chest, abdomen, spine, knees and toes. The mucous membrances showed no bronzing. His speech is rather monotonous. An examination of his heart and lungs was negative. He gives a history of hook worm infection in the past, for which he has taken treatment. Once he vomited a round worm. Since he has been in the hospital his bowels have been irregular, alternating between spells of constipation and diarrhea. His sleep has been poor. He has complained at times of pain in the lower abdomen. For some time he refused to take food, or vomited when he took it. He also complains of shortness of breath and a choking sensation in eating, of a sense of gas on the bowels and sick

headaches. At times he has spit up a little blood after eating. This was only in streaks and occasional.

Addison's disease is supposed by some to be due to tuberculosis of the adrenal glands. No focus of tuberculous infection can be found in this case; however, the patient has a brother, whom I have never seen, who probably is tuberculous. Dock, in Osler's System of Medicine, describes reflex changes in some cases which are due to spinal tract degeneration, and also mentions that mental symptoms, especially insomnia and mental confusion, have been observed. I can find no mention of imperative ideas. It is possible that this patient's irresistible desire to run was of sexual genesis and was a replacement of a sexual impulse. He has, however, shown no sexual proclivities since he has been in the hospital . His genitals are of normal development except for the lack of hair. This body hair deficiency is distinctly a hypo-adrenal manifestation. This patient has also shown the mental symptoms of irritability, fatigue and emotionality. Confusion was not observed.

The boy has greatly improved but the prognosis is doubtful. The treatment has been general attention and adrenal gland extract grs. ii, three times a day.

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COMMENT ON DR. TUCKER'S CASE

**Dr. William Wallace Behlow, San Francisco:** This very interesting case presents certain symptoms which require considerable study. The youth of the patient, his mental symptoms, and the apparent absence of any demonstrable tuberculous focus elsewhere in the body are of more than usual interest.

In considering the youth and the mental disturbance, one must remember that certain psychoses are very likely to appear during adolescence. It is there-

fore possible that the mental deterioration may be merely an associated condition. On the other hand, Addison's disease frequently presents cerebral symptoms, either in mild or severe form .

It is now believed by many physicians that the adrenal glands in this disease are congenitally abnormal and are therefore more likely to be affected by any infectious process than would be the case were they normal organs. If we accept this conception of the disease, it is not difficult to believe that other organs may be the site of congenital disturbances, and if such be the case, it is possible to consider the mental signs as merely a manifestation of deficient cerebral function.

Viewing the case from a different angle, we know that in this disease the entire gland frequently suffers from the degenerative process. Remembering the relation between the development of the adrenal cortex and that of the brain, we may consider that these two distant parts of the anatomical structure, have some interrelated functions. If, therefore, the adrenal cortex is in a state of hypofunction, it is not unlikely that certain exciting or inhibitory influences on the brain are lacking.

The apparent absence of tuberculosis elsewhere in the body is important. It is unfortunate that intradermal tuberculin tests were not recorded, inasmuch as through this procedure we could have determined the presence or absence of tubrculosis. When one thinks of Addison's disease, the pathologic picture of caseation and calcification of the adrenal glands comes to mind. It is important to remember that all cases of this disease are not tuberculous, and it is evident from this fact that we must search for the etiologic factor in the absence of other signs of tuberculous infection.

Another interesting feature of the case is the absence of any anemia. In fact the red corpuscles are increased in number. The reason for this condition of the blood is not clear. No mention of the type of

leucocytes present in this case has been made. While a differential count is not necessary, it is desirable for this reason, namely, the frequency of an associated status thymolymphaticus in Addison's disease. Roentgen examination of the chest and of the kidney regions might have shown pulmonary tuberculosis, a large thymus and calcified adrenals. I wish to emphasize this last point. During the past year, I have been looking for thymus enlargement in all ductless gland dystrophies and have found it in several cases. Of still greater interest is the finding of shadows above the kidneys showing evidence of calcification of the adrenal glands. This was beautifully demonstrated in a case of hypoadrenia which I saw some weeks ago.

If we can have reports of cases such as the above, we will soon discover what we have to forget and what we have to learn about the endocrinopathies.

**Dr. Henry R. Harrower, Los Angeles:** This case report contains several points which demonstrate the truth of the statement that "there cannot be a disorder of one of the glands of internal secretion without some associated disturbance of one or more of the others." The patient shows a number of evidences of disorder of others of the endocrine glands than the adrenals. For instance, the dry skin and reduced perspiration would remind one of thyroid insufficiency, the absence of axillary hair and scant pubic hair coupled with the remark later that the sex impulses were diminished draws attention to a possible pituitary factor (though it is granted that it may accompany hypoadrenia as Doctor Tucker remarks) and it would be interesting to learn the findings of sellar radiography.

The greater our information on the subject of the internal secretions, the less frequently will we be able to make positive, named diagnoses. This may seem to be a contradiction, but it is none the less true. Take as an instance the condition under discussion—Addison's disease or organic adrenal disease with chrom-

affin insufficiency. It is impossible for so important a pair of organs to be the seat of destructive processes (not compensated by an hypertrophy or increased functional capacity of the remaining sound gland substance) without simultaneous functional disturbances in the gonads, thyroid or others of the glands of internal secretion. The typical toxic asthenia in these cases doubtless is of adrenal origin and, too, the adrenal part of the picture may be most prominent; but all the factors which go to make up the syndrome described by Addison are not purely adrenal, save indirectly. Herein lies the complexities of endocrinology.

From my own standpoint the diagnosis would not be exactly Addison's disease, but rather pluriglandular insufficiency or endocrine dystrophy with prominent adrenal manifestations; and the treatment would take this into consideration and include other organotherapeutic extracts than the adrenal substance now being given. It has been my experience many times to see a case in consultation and to suggest that one or more organotherapeutic preparations be given in addition to the one which may have been taken before I saw the patient, and more than occasionally decided additional benefit followed the change from mono- to pluri-glandular therapy.

**Dr. Walter Timme, New York:** The picture presented by Dr. Tucker is graphic and extremely interesting, but it lacks certain elements necessary to differentiate it from conditions allied to Addison's disease. The one important syndrome known as vagotonia seems to fit quite as well as Addison's disease to the case. Here we also have the slow pulse, low blood pressure, slow respiration, vasomotor mottling of the skin of the extremities, vomiting, alternate constipation and diarrhea, and pain in the abdomen that Dr. Tucker's case presents. One etiological factor that speaks in favor of this diagnosis is the fact of a previous invasion of parasites—a most prolific cause of vagotonia. The one symptom that apparently is

opposed to it is the bronzing of the skin. And yet the bronzing has left the mucous membranes free—a point of great significance and one upon which many authors insist before making the diagnosis of Morbus Addisonii. On the other hand we frequently see mottling of the skin alone in persons of uncleanly habits, such as farm hands are apt to be. Another point is the normal number of red cells in the blood—rarely found in Addison's disease.

As for the mental states accompanying this affection of the adrenal glands, they may be said to be of the retarded type. There is mental sluggishness and hebetude usually and rarely the compulsive character such as this boy shows in his attempts at flight. The patients usually show a desire to remain abed and at rest. And yet, it is almost imperative to view and examine such a case as this personally, before coming to a definite conclusion satisfactory to one's self. For, after all, diagnosis depends upon the correct interpretation of the signs and symptoms which one must elicit himself—each sign has for the individual evoking it a special significance. So that Dr. Tucker may be correct in his diagnosis and have a picture of his case quite different from the one that the writer gleans from the case report.

# AN ENDOCRINE INTERPRETATION OF THE DENTAL APPARATUS

By D. M. Kaplan, M. D., New York City

(Director of Laboratories, Neurological Institute, N. Y.)

THERE is not the least doubt that the glands producing internal secretions exert an influence upon the exterior of the individual. Although the uninitiated still may consider certain individual peculiarities as accidental, the endocrinologist knows which organ, or organs, were instrumental in the production of these seemingly accidental phenomena. To ascribe a certain bodily appearance to accident is a confession of ignorance which, however, is becoming less frequent the more one studies the mystic forces of the endocrines. The study of their functions can not be severed from the study of these glands, so much so, that one may justly call this specialty an investigation of the "compensatory dynamics of the endocrines in health and disease."

To understand the compensatory workings of the endocrines is to know "internal secretions"; and to be able to translate it into terms of physiology and pathology is to know how to handle your patient from an endocrine point of view. There are many external manifestations resulting from the work of the endocrines that have been carefully studied, many that are only superficially known, and still more to be discovered in the future. To the endocrinologist a pigmented mole is not an accident, nor the moustached female of twenty-five, nor the soft pulse at eighty, nor the high blood pressure at thirty, nor the enlarged non-infected tonsil. It is the why and wherefore of a peculiarity that is the constant question before the endocrinologist, and very often the answer

is radically opposed to orthodox allopathic thought. Therefore the uninitiated may be perplexed by the stand taken by the student of compensatory dynamics, who argues against the reduction of a high blood pressure in a certain patient, or the removal of the tonsils in another, and yet he may offer very sound reasons for both conclusions.

In his endeavor to arrive at the truth, the student of "compensatory dynamics" takes into consideration the fact that certain infections have an affinity or, as I have designated it, a "tropism" for certain glands with internal secretion. For instance, it is known to all that mumps is an infectious disease that often attacks the gonads. It has been noted that diphtheria and typhoid have a tendency to cripple the adrenals, so that mumps is known as a gonado-tropic infectious disease, while diphtheria is adreno-tropic.

There is also a definite tropism between endocrine disturbances and the dental apparatus. Ewan Waller, of Birmingham, England, has very definitely associated the teeth in children with the thyroid function. It seems that the glands with internal secretions play an important role not only in the structural, but also in the physio-chemical economy of the individual. A great many of the unclassified subjective disturbances formerly designated as neurasthenia, neurosis, or hysteria, and lately as vagotonia, can be more justly ascribed to an aberration or a disturbance in the compensatory dynamics of the endocrines. The thorough investigator of the constitution of an individual in health or disease takes into account the phenomena not only as pictured in our books on diagnosis, but also the time of day or night, the amelioration or intensification of symptoms in the evening, its involvement of the right or left side of the body, and he dif-

ferentiates where the same complaint appears in the juvenile, adult, or senile individual.

There are a great many points dismissed by the uninitiated as insignificant, which the endocrinologist employs to advantage in building up a picture of disturbed equilibrium in a patient. The peculiarities of the dental apparatus is one of them.

**Thyrodontia.** It is a fairly well-established fact that the calcium metabolism is governed chiefly by the thyroid apparatus, and secondarily, by the rest of the endocrines. The alkalinity of the saliva to a certain extent depends upon calcium salts. It is to be seen how a disturbed endocrine equilibrium could bring about dental decay by a disturbance in the calcium metabolism balance, particularly in children, who depend upon their thyroid and thymus more than the adult and senile. The calcium being deficient, the acids from food decomposition are not neutralized, and the dentine consequently suffers, this being one of the stages in the complete breaking down of the tooth. In children particularly, a well-balanced thyroid and sound teeth go together. If the thyroid is not performing its duties properly, the tooth to suffer first is the molar. The submaxillary saliva is said to be richer in calcium than the parotid, and in view of the fact that the molars lie behind the duct their supply of immunizing saliva is less than the front teeth, and hence, in case of calcium deficiency, they succumb first. This is manifestly apparent in the longer life of the lower front teeth as compared with the upper, the latter not having the constant salivary bath enjoyed by the lower teeth. This is very characteristically displayed by the woman with an exhausted thyroid, due to repeated pregnancies, who invariably loses her upper incisors. Of course in such

women the other endocrines enter into the mechanism conducive to the dental loss.

To start with, thyroidal teeth are distinguished by their slender frame, they are thinner, more transparent and graceful, and their color tends toward a bluish-gray-white. Children and married women with such teeth can be saved a great deal of dental trouble by the discreet and timely administration of thyroid extract. The frequency of the therapeutic display depends entirely upon the case and the acumen of the physician.

In the multipara the dental situation from an endocrine point of view is only partly thyroidal. The interplay and compensatory work of all of them are necessary to help her through this physiologic symbiosis, and if the woman is deficient in any of the endocrines she will display not only dental changes, but all kinds of other objective and subjective manifestations depending upon the glands or gland involved. The falling out of the upper incisors independent of decay, bears a distinct pituitary stamp, and one may say that the maxillary sockets become too large in some pregnant women, and that the root is not firmly implanted in such a jaw, at this episode of partial transient physiologic acromegaly. It is the duty of the discerning physician, as well as the dentist, to guard against irreparable loss, disfigurement and suffering of patients by a timely use of thyroid extract in cases of dental caries or late irruption, as well as in gestations that promise injury to the teeth.

**Pituitodontia.** Many individuals who are free from complaints that would compel them to seek a physician's advice, are the possessors of teeth characteristic of the acromegalic. The owners of such teeth need not develop acromegaly, nevertheless they

must be regarded as potentially pituitary. Chronic frontal headaches and the slightest limitation in the temporal visual fields, require very earnest attention and extremely judicious endocrine therapy, for at such a stage one might hold out some hope of deferring the advent of the full-fledged acromegalic picture. Increase in size of the acral parts is the chief objective sign of this disease, and the pituitary is the gland responsible for its appearance.

It must not be forgotten, however, that not only an increase, but also a very marked diminution in size, belong to the activity of the pituitary gland; so that giant and pigmy are endocrinologically related. The same applies to the teeth. The average pituitary dental arrangement shows large square teeth; more often than not the upper middle incisors are spaced (trema) and the rest of the teeth may share in their separation, stopping at the bicuspids. On the other hand, marked overcrowding is a feature which also belongs to the department of hypophyseal activity, so that one is frequently confronted with a situation requiring great care in endocrine interpretation. The gestating female has been referred to before, but it must be reiterated, that the falling out of the incisors, particularly the lateral ones, has a double meaning.* At present let us not forget that the middle upper incisors are pre-eminently the teeth closely associated with direct primary pituitary function. This does not signify that the individual has a pituitary abnormality incompatible with perfect health; it may show itself in anybody with accepted hypophyseal markings, such as being very tall or very short, having a very large head, particularly in

*This will be brought out in the paragraph on gonadodontia.

the frontal part, or manifesting a tendency to adiposity in the young or adult, with or without hypogenitalism. It may accompany the feminine type of man, who shows his abnormality in his teeth only, and his sexual anomaly in his psychanalysis.

**Gonadodontia.** Individuals with a gonadotropism may give in their history an attack of mumps during childhood. The close relationship between this contagious disease and the genital glands is established by the frequent involvement of the ovary or testis in a complicating inflammatory reaction. It is not necessary that the individual previously having had mumps should present ear marks of a definite gonad disease, he may yet show them in the future, or not at all. This depends entirely upon the compensatory work of the rest of the endocrines.

In all endocrine manifestations not only the some, but also the psyche is influenced.* Besides these psychic attributes most of them show definite somatic stigmata, of course not all of them, the exceptions here as elsewhere serving to establish the rule.

In the gonadotropic individual the dental apparatus carries a very striking ear mark of the tropism. If the middle upper incisors carry a message from the pituitary, the lateral upper incisors certainly do the same from the gonads. So that when the gonads are teratologically ab ovo definitely abnormal, one is sure to find some abnormality in the upper lateral incisors. The relationship, if any, is a crossed one, so that the right upper lateral incisor may point to the left testis or ovary, and vice versa.

It is also to be noted that the greater the devia-

*This is, perhaps, seen in the irritable thyreotrop; the gentle and kind giant or obese person—pituitotrop; the assertive, hairy adrenotrop; the juvenile or childish thymotrop and the bashful or secretive gonadotrop.

tions from normal, the more definite the markings in the dental department, so much so, that the lateral incisors, as the result of a marked gonad defect, may not have irrupted at all. Such a dental situation is rare indeed, so is also the clinical condition presented by the patient who has it. Here is a situation that the gynecologist could profit by, and the surgeon add another sign to the significance of right sided abdominal pain. Such a pain is usually ovarian,—when the left upper lateral incisor is faultily implanted, showing the mesial edge of the tooth anteriorly, and protruding in front of the middle incisor. The teeth presumed to be connected with the gonads (upper lateral incisors) carry the stamp of ovarian or testicular abnormality in their size, shape, or implantation.

The ovary should always be suspected where pelvic pain is manifested in a patient whose lateral incisors are abnormal. In the male, small stumpy laterals bespeak sexual impotence on a physical basis,—many gonorrheas, prostatic insufficiency, and chronic strictures. In such an individual one may obtain the history of mumps, and if he had a right-sided orchitis or epididymitis, more often than not his left upper lateral incisor will be found differing from the normal, taking his entire dental apparatus as a standard of comparison.

On rare occasions the compensatory work of the other endocrines is so well-adjusted that the dental anomaly is obliterated, and gives no clue to the existing gonadopathy. There are, however, other external signs from an endocrine point of view that would direct attention to the existing state of affairs. As the dental apparatus is the subject of this paper, the other signs will not be discussed.

There is a dangerous tendency among endocrinol-

ogists to designate with peremptory precision that this or that organ is involved, and is responsible for the endocrine picture. Very often the external manifestations are caused by another gland whose function it may be to bring about phenomena on the surface of the patient, such as, for instance, the adrenal system; and some students may be carried away by this easily demonstrable, superficial appearance, and be led to assign to the objective findings the place of first importance; whereas the adrenals have simply acted in response to a call from some other gland. The gonads always require adrenal help in performing their work, and when they do not come up to the physiologic requirement, be this in the form of under or over activity, the adrenals are then called upon for additional assistance, resulting, secondarily only, in manifestations appearing on the skin, mucous membranes, hair, etc. The primary, ab ovo, situation can be read from the teeth, and the gland responsible for the trouble more often than not, can be unerringly named and proper therapy suggested. It is remarkable how readily the patient responds when the proper drug is prescribed, but here, as elsewhere, the futility of attempting replacement therapy in some cases must be thoroughly gauged.

A young woman suffering from the torture resulting from a complete oophorectomy cannot be benefited much by ovarian extracts, be it the whole gland or the luteal portion. In such cases one must be able to read intelligently the symptomatology, and curb as much as possible the pituitary compensation, for in such cases this is the gland that may be causing much of the subjective discomfort. If the pituitary, however, is not capable of compensation, or is only partly able to assist, the adrenal and thyroid systems

are employed to overcome the deficiency. Depending upon the fitness of these glands one will have a predominating adrenal or thyroid symptomatology. Therapeutic success depends entirely upon our ability to recognize the vicarious execution of functions by glands with a different purpose.

**Adrenodontia.** It is to be conceded that the ability to perform better work requires better tools. In biology this is everywhere evident. From times immemorial the longer and sharper tooth was part of the outfit of the pithecanthropus, whose survival was assured. Such a specimen was perhaps also the hairiest of his tribe. As time advanced and the necessity for using the teeth in offensive and defensive existence became secondary to the special development of the thumb and hands, the chief fighting teeth, the canines, became shorter, and in some very peaceful members of our semi-simian ancestors, also less sharp. With the greater use of the hand came the perfection of that part of the brain that serves as the storehouse for memories. These memories became the heritage of the future man, and with the greater specialization of the hand, the teeth were gradually discarded as weapons of defense and offense. The emotions in a state of offensive rage still cause the display of teeth, although one does not use them.

Vasomotor force and the tone of muscles depends upon the proper work of the adrenals. Only when these glands work better than the others, is it possible to think of the enduring prizefighter. When the pituitary is equally well-adjusted, one has the heavy weight champion type. But the ability to scrap, whether curbed by education or environment, or not, is indelibly marked in the canines. As one of our ancestors would have learned by experience that his

short and blunt canine was no great weapon in a fight, and would have become the champion of peace instead of conflict, so also the present man prefers discretion to valor because of inadequate adrenal endowment or, as one may term it, lack of biologic equipment for strife. Whether man or woman, both show in a long sharp canine an atavistic remnant of a bellicose progenitor, and upon proper provocation justify the above contention.

Very often the large and sharp canine in a woman bespeaks the aggressive agitator, public speaker, or militant suffragette. Some of these women studied from the point of view of biologic balance possess other endocrine markings, showing that they are not women to the full extent that nature intended the average woman to be. The woman whose skin is rough, who finds pleasure in curbing wild horses, who cares not for the duties of home life, and who is an expert administrator (purposely using the masculine) must give up a certain amount of natural feminism in order to be able to enjoy and accomplish the above things. Very often with such traits goes a masculine hand, a moustached lip, a large pointed canine, and a deficient gonadont. The sexual psychopath could be detected by a study of his dental apparatus, and the endocrine therapist might supply the glandular extract that would give a more natural trend to the twisted psyche of its possessor.

The spinster who truly rejoices in her single blessedness does not do so from choice, but rather from her innate promptings. Being less of a woman than her well-balanced sister, she does not require the society of man, and frequently shows her genuine distaste for such company by an appropriate remark. In her pursuits she wants to dominate, and frequently

fills with credit a position requiring great virility. She abhors the evening gown, and wears clothes of a masculine type, low heels, no corsets, side pockets, collar and tie.

The male counterpart with short, stumpy and dull canines gives up some of his primordial male aggressiveness, and becomes the Jacob instead of the hairy Esau. The kitchen is his place. He can sing in high notes, never a basso, and has the greatest inward storms when the time comes for him to propose marriage to his heart's choice. Such a man stands a poor chance of being accepted by a girl well-balanced from an endocrine standpoint. It is the one who will not enlist to help defend his country, but will offer a thousand and one reasons why he should not fight, that war is a reversion to barbaric times, etc., etc. Such men are afraid that a gun might go off, and in business are equally nonprogressive. The eternal clerk, messenger boy, cook, and other nonprogressive occupations are theirs. Endurance, progressiveness, discovery, go hand in hand with an endocrine system that is perfect, and a canine tooth that fears not to face antagonism in any shape or form.

The adrenodont in its structure gives us a clue to the adrenal balance of the individual. There is another characteristic of the adrenal tooth, the color. The grinding surface of such teeth shows a marked reddish brown coloration, and although softer in texture than the thyroid or pituitary variety, they have a greater degree of endurance. Here again is a hint of the ability of adrenal secretion to protect. Old men or women will show short teeth still in a very good state of preservation and most conspicuously marked with this reddish brown pigment. Younger people with such teeth can be assured of

their lasting character, and it is astonishing to note how some of them remain intact regardless of the lack of care and the thick wall of tartar that surrounds them. Age or the ability to grow old goes hand in hand with proper adrenal work, of course with the assistance of the other endocrines, and so adrenal markings in the form of pigment insures not only the life of the tooth, but also its possessor. Individuals who become patients on account of improper adrenal work may show this peculiarity in their teeth also, the markings here indicating the gland affected as well as suggesting the proper therapeutic course to pursue.

**Thymodontia.** The tooth of the baby is bluish porcelain, thin at the grinding edge, and translucent in that part. The tooth in some children shows a tendency to scalloping at the grinding edge. This trait may outlast the baby and in rare occasions be found in the adult. The other infantile characteristics may go with it, such as a red cheek, an excellent digestion, and a tendency to diarrheas. The finding of such teeth in the adult points to the youth of the individual, regardless of years. In this persistence of juvenile characteristics one must always weigh the compensation offered by the other glands with internal secretion.

The purpose of this communication will have been accomplished if the physician and dentist will begin to see in the dental apparatus a greater purpose than the sole function of mastication. When fully studied upon lines suggested above, a volume of facts will be discovered that heretofore may have many times been entirely overlooked.*

*The work in this communication is gathered from the observations and studies pursued by Dr. Joseph Fraenkel and his followers, who are students of constitutional medicine, particularly as applied to therapeutics.

COMMENTS ON DR. KAPLAN'S PAPER

**Dr. Isador H. Coriat, Boston:** I have read Dr. Kaplan's paper with considerable interest as it opens up a new field of investigation in endocrinology. The recent appointment of a neurologist to the Forsyth Dental Infirmary, whose work will be particularly directed to the influence of the ductless glands on the growth of children, is in harmony with Dr. Kaplan's investigations.

We have noted at this institution that in children who show hypothyroidism or even slight signs of thyroidal insufficiency, without the necessity of going so far as cretinism, show certain disturbances in the nutrition of the teeth; but it will be necessary to have a large amount of data at hand before we can assert definitely that the relationship is always one of cause and effect. However, the fact that the teeth improve in their nutrition under the administration of thyroid gland, leads one to feel that he may be working in the right direction.

The abnormal spacing between the teeth has been a sign long known in acromegaly, and possibly in the future there may be pointed out other dental disorders which are the result of disturbances in hypophyseal activity. On the whole, while the relation of the ductless glands to the teeth is a stimulating subject, yet we must be very cautious in our endocrinological interpretations along these lines for some time to come.

**Dr. E. G. Zabriskie, New York City:** The manuscript of Dr. Kaplan's article on the Endocrine Interpretation of the Dental Apparatus has been read with care and interest. I believe that there is a great deal to be said in favor of his contentions; though his use of the term "tropism" is especially limited, as he bases it on the affinity which certain infections have to certain glands of internal secretion, and this is not warranted. His references to the instances of affections of the glands of internal secretion resulting from infectious disease as inflammation of the gonads ac-

companying mumps, and the tendency of diphtheria and typhoid to cripple the adrenals, are well known; but I believe it is wrong to designate these as "tropisms."

Then again the relationship between the lateral incisors and the gonads to my mind is not at all well established as yet. His contention about the contralateral pain in the region of the ovaries in individuals whose lateral incisors are either misplaced or badly affected, is not yet well enough established to be accepted unconditionally. Since my attention has been called to this I have noted its presence in several instances, but it is also true that in others I have seen the same thing where the canines were not affected.

The author's remarks about the dangerous tendency among endocrinologists to designate with peremptory precision the involvement of this organ or that, and its responsibility for the endocrine picture, is well taken. Perhaps it is only due to our present lack of more precise proofs of these statements but, as yet, we are too close to the threshold of the entire subject to accept them without further careful study.

# THE RELATION OF THE NERVE SUPPLY OF THYROID GRAFTS TO THEIR ENDOCRINE ACTIVITY

By Dr. E. Kummer, Geneva, Switzerland

**(From the Laboratory of Physiology of the University of Geneva.)**

IT is generally believed that the thyroid secretion is subject to the influence of the nervous system, and Ascher has shown that the influx of secreto-motor influences is carried by the laryngeal branches of the pneumogastric nerve. Since this is so, should this not compromise or at least alter the endocrine function of a thyroid graft which is naturally separated from its nervous connections?

Experimental investigators have established the fact that a graft will supply the total endocrine function of the normal thyroid gland, irrespective of its location; but this opinion has found some contradiction amongst surgeons. Some of them, taking the logical but purely theoretical view, have stated that in order to give the maximum opportunity for a graft to take it must be made only in the cervical region in order to give the graft the opportunity of reestablishing its more or less normal nervous connections so that its secretory functions may not be compromised.

Modern research into the nervous mechanism of muscles, especially recent surgical procedures, has given a certain suggestion of reality to this question. If it is possible by nerve implantation to reestablish the contractility of a paralyzed muscle, should it not, perhaps, in the same manner, help the functional capacity of a graft of thyroid tissue? With this matter in view we have carried out some investigative work the results of which are related here.

The functional value of thyroid tissue may be established by three main tests of which only one in our opinion is of paramount value.

1. The chemical test or research into the chemical characteristics of the thyroid secretions.—A number of chemical bodies of more or less purity have been secured from the thyroid gland. Among these are certain lipoids, a lipolytic ferment, choline, and particularly the iodin-bearing protein substances including iodothyrine (Baumann), iodothyroglobulin (Oswald) and the alpha-iodin more recently isolated by Kendall.* The specific thyroid action appears to be identical, or at least very decidedly similar, to that of the iodized thyroglobulin, and in this substance the iodin content plays a preponderant role since the same thyroglobulin deprived of its iodin is likewise deprived of its specific action.

So far as the iodin content of thyroid extracts is concerned, this is a very variable factor. Generally speaking the quantity of iodin is in proportion to the amount of colloid substance. Goiters without colloid do not contain iodin. The colloid goiter is really a sort of iodin reservoir for the organism.

Following a hemistrumectomy, A. Kocher has found that the quantity of iodin accumulating in the remaining lobe was doubled. According to this same author, goiters in Basedow's disease show a notable reduction, or at least a large variability, in their iodin content. This last also depends upon the age, for absence of iodin in the fetus and the new born is progressively increased from one to thirty years, diminishing after 40 years. The iodin content depends also upon the species of animal. The herbivorous show a

*It so happens that a comprehensive resume of Kendall's work appears in this issue, page 153.

maximum, the carnivorous a minimum, and the omniverous an average amount, of iodin.

From the above, despite their obvious interest, it is evident that the results of the chemical examination of thyroid tissue will not furnish information of a character which will enable us to prove conclusively the functional value of a thyroid gland, or a part of it.

2. Anatomical examination.—A thyroid graft to be successful, must secure a good vascularization with good conservation of the follicular apparatus and particularly of the normal epithelial cells, both as regards form and relation to one another, and retaining the colloid substance in the center of these follicles or in the perifollicular lymphatics. Such a graft thus presents manifest signs of functional activity; but in order to appreciate the degree and usefulness of its internal secretion really we have but one conclusive proof and this is the biological test.

3. The biological test, i. e., the study of the results of the removal of the graft.—The proof that normal internal secretory powers have been retained by a graft lies in its physiologic service to the organism. If an animal is thyroidectomized and successfully grafted and then dies in a state of thyroprivia following the extirpation of the graft, we are justified in assuming its endocrine value. We have found in our experiments that this biological test parallels the anatomical examination.

The dog, or better still the cat, offers the greatest facility for research of this character, for of animals convenient for laboratory study these are less likely to show aberrent thyroids and thus are more easily subjected to total thyroidectomy. On the other hand, the characteristic consequences of extirpation of the gland are not long in showing themselves. Because

of the very intimate connections present in the cat and the dog we really perform thyroparathyroidectomy and not simple thyroidectomy when we operate upon these animals and the tetany resulting from these operations lasts from six to eleven days. It is by judging the symptoms of tetany that we are able to determine the functional value of a thyro-parathyroid graft.

Dog No. 1. Adult.

July 3. Total extirpation of the thyroid and parathyroids. Immediate graft of both lobes into a pocket of the omentum.

July 5. Slight stiffness in the back legs.

July 6. Trembling and muscular tremor.

July 7. General convulsions.

July 8. Repeated convulsions.

July 9. Death, with nothing in particular autopsy. Examination of the epiploic graft showed a small nodule of firm consistence; slight fluctuation. When incised a mere indurated shell was seen, the center of which was soft greyish tissue microscopically showing a peripheral fibro-fatty structure, an inflammatory zone containing numerous leucocytes and the whole central part showing very indefinitely the original thyroid structure.

Dog No. 2. Young.

July 3. Thyroparathyroidectomy. No graft.

July 5. Prostration; no stiffness.

July 6. Slight tremor.

July 7. General muscular tremor.

July 8. Sudden spasmodic movements with subsultus. No convulsions.

July 13. Death.

Dog No. 3. Young, with slight goiter.

July 20. Hemithyroparathyroidectomy (right). Immediate graft of one-third of the lobe removed, inserted into the structure of the goiter in contact with both vessels and nerves. Muscular suture to fix the graft in place.

July 28. Slight suppuration. Bichloride solution locally.

August-September. Perfect health.

Oct. 14. Hemithyroidectomy (left). Noticeable hypertrophy of left lobe, weight 14 gm.

Oct. 16. Death, cause unknown. No cramps or convulsions. Autopsy: Graft in right side presents normal thyroid tissue. A little hemorrhage into wound in left side. Microscopic examination showed the thyroid tissue to be normal with good vascularization and an abundance of colloid sub-

stance. No trace of nerve proliferation. Parathyroid tissue not found.

Dog No. 4. Young.

July 23. Hemithyroparathyroidectomy (left). Implantation of graft into thyroid notch under the superficial cervical aponeurosis.

Aug. 20. Suppuration in wound.

Oct. 23. Perfect health. Right lobe of thyroid (with parathyroids) removed. No evidence of hypertrophy. Implantation of graft (total) into great omentum (Cristiani's method).

Oct. 26. Dog found dead, not having presented any signs of tetany. Autopsy: Abscess at graft; cicatrice at site of first operation. Microscopically this latter showed no thyroid elements; in the second (omental) graft much leucocytic infiltration with some remaining thyroid tissue seemingly quite normal.

Dog. No. 5. Adult.

July 28. Left hemithyroparathyroidectomy. Immediate graft of whole piece into omentum.

Sept. 27. Perfect health. Right lobe removed, apparently normal.

Oct. 1. Slight exhaustion. No trembling.

Oct. 4. Tremor, no convulsions. Animal eating well, in good condition.

Oct. 14. Excision of graft. During ether anesthesia generalized trembling.

Oct. 22. Stiffness.

Oct. 23. Very violent perpetual trembling, stiffness of legs, back bent, trismus, cannot eat. Death. Autopsy: Scar in cervical region, no trace of thyroid tissue therein. Nothing abnormal in peritoneum save slight local suppuration. In omental graft much leucocytic infiltration, slight evidence of follicular tissue but great infiltration obscures appearance of thyroid structure.

Cat No. 1. Age about two years.

July 28. Right hemithyroparathyroidectomy with graft into neck in immediate contact with suitable vessels and nerves.

Oct. 21. First operation site all healed. Health good.

Oct. 23. Left side operation. Entire lobe (of normal appearance) then transplanted into great omentum.

Oct. 30. Abdominal suppuration (localized). Slight exhaustion. No stiffness.

Nov. 4. Persistent exhaustion. No cramps.

Nov. 30. Perfect health.

Dec. 2. Excision of cervical graft. Not certain that thyroid tissue is found; microscopically not definite.

Dec. 30. Dysphagia, no stiffness or cramps.

Jan. 22. Death with no signs of tetany. Autopsy: Nothing in particular. Cause of death supposed to be dysphagia. The omental graft was lost.

Cat No. 2. About one year old.

July 30. Right hemithyroparathyroidectomy. Whole piece engrafted into base of right ear.

Aug. 30. Healing. Perfect health.

Sept. 27. Left hemithyroparathyroidectomy.

Sept. 30. Stiffness of legs.

Oct. 1. Stiffness, trembling, dragging of back legs. Crisis of convulsions, tonic and clonic seizures, difficult respiration, eyes partly closed, consciousness lost. (?)

Oct. 3. Death. Autopsy: Nothing unusual. Microscopic study failed to discover trace of the graft.

Cat No. 3. One year old.

July 30. Right sided operation as before, with graft (total) into base of right ear.

Aug. 30. Healing, good health.

Oct. 22. Left lobe, etc., removed, grafting a portion of this into omentum.

Nov. 4. Healing with good health.

Dec. 2. Amputation of ear, with graft.

Jan. 27. Recovery, good health.

Jan. 28. Excision of other graft.

Feb. 1. Exhaustion; cannot eat.

Feb. 3. Trembling, muscular tremor (general), no convulsions.

Feb. 6. Death. Autopsy negative. Microscopic: (1) Ear. Thyroid follicles well preserved, no colloid material. Leucocyte infiltration. No parathyroid tissue noted. (2) Omentum. Very beautiful specimen of thyroid tissue with normal follicles, abundant colloid, rich blood supply and slight leucocyte infiltration. Parathyroid tissue uncertain.

**Resume.** We feel justified in answering the question set forth at the beginning of this article with the following remarks:

1. We have not observed any new formation of nerves in thyroid grafts.

2. The reestablishment of the function of the graft has not been any better when implanted in the neighborhood of the pneumogastric or its branches than when made in any other part of the body.

3. In spite of denervation the graft by itself alone

is able to satisfy the need of the organism (of the cat or dog) for the thyro-parathyroid internal secretions.

**Conclusion.** Whatever may be the importance of the role played by the autonomic nervous system as the secreto-motor nervous regulator of the thyroid body, the thyroparathyroid graft without any nervous connection is capable of furnishing the internal secretion which suffices to maintain health in both the dog and the cat. From a practical point of view attempts to ennervate grafts are wanting in interest.

Judging from the well-known fact of the interchangeability of thyroid extracts of man and of certain animals, what we have found in the dog and the cat has every good reason to be true in man.

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# BOOK REVIEWS

THE SEX COMPLEX: A Study of the Relationships of the Internal Secretions to the Female Characteristics and Functions in Health and Disease. By W. Blair Bell, B.S., M.D. (Lond.), Gynecological Surgeon to the Royal Infirmary, Liverpool; Hunterian Professor, Royal College of Surgeons, England, etc. 1916. Pp. 233. New York, Wm. Wood & Co. $4.00.

Gynecologists, of all physicians, are vitally interested in the study of the influence of the glands of internal secretion, for so many functional gynecological disorders are of endocrine origin. Many of us think that we are beginning to know something of what Blair Bell has aptly termed "The Sex Complex," and undoubtedly our knowledge is becoming more comprehensive and more useful. But the subject is indeed a "complex" and only its intensive study in the laboratory and the clinic will make possible much greater progress in the future.

For many years the investigations of the author of this book have been leaning towards endocrinology. To him the profession is everlastingly indebted for the introduction into therapeutics of the posterior pituitary principle.* He has also enlightened us very materially as to the role of calcium in the organism and has demonstrated the importance of the hormones in regulating the calcium balance in health and disease.

In this well-planned and well-written book Blair Bell has assembled the results of his years of study.

*The first paper on this subject was published by Blair Bell in 1909: Blair Bell (W.) "The pituitary body and the therapeutic value of the infundibular extract in shock, uterine atony and intetsinal paresis," British Medical Journal (Lond.) 1909, ii, 1609.

He has made the "dry bones" of the experimental work become alive by his well-balanced philosophy. He has made the clinical side intensely practical by his evident wealth of actual clinical experience.

This is not "a difficult book to read," for there is not a barren page in it; and since the study of the endocrine glands in woman is such a fertile field for entry by practical physicans, we cannot but thank the author for having given the profession such a useful vade mecum.—H. R. H.

THE NEWER METHODS OF BLOOD AND URINE CHEMISTRY, by R. B. H. Gradwohl, M.D., and A. J. Blaivas of the Gradwohl Biological Laboratories, St. Louis. 1917. Pp. 240. St. Louis, C. V. Mosby Co. $2.50.

This most recent addition to the list of laboratory text books is indeed welcome, for in the past two years clinical diagnostic procedure seems to have advanced further than in any similar period in the past.

The book is reviewed here not merely because the senior author is a charter member of the A. S. I. S., but because endocrinologists, of all students of medicine, are vitally concerned in the chemical relationship of the body in health and disease.

The early modifications of endocrine function without a doubt are responsible for blood and urine changes; some of these have yet to be worked out, while the recent advances in blood chemistry now make it possible for the diagnostician to be much more certain of his findings.

Naturally so important a book will be welcomed by our membership, and its perusal will serve them well.—H. R. H.

# THE LITERATURE ON THE INTERNAL SECRETIONS

## GENERAL SUBJECTS

**Over-Activity of Vagus System and Anaphylaxis.** Smith (J. H.) Jour. Nerv. & Mental Dis. (N. Y.) 1916, xlv, 26.

By vagotonia is meant the clinical appearance of chronic or recurrent symptoms recognized as manifestations of over-activity of the vagus system.

The two parts of the vegetative system, the sympathetic and vagus, exert a constant balance on one another. The normal excitant of the sympathetic is adrenalin; that of the vagal system is not known.

The fundamental fact in anaphylaxis is proteolysis. The vagus system and muscles supplied by it are chiefly influenced. Anaphylaxis manifests itself through vagus irritation.

Toxic influences, especially anaphylatoxins, may be considered as underlying the vagotonic state. Definite proof exists of the anaphylactic nature of certain cases presenting vagotonic manifestations, viz., parasitic infestations, food idiosyncrasies, asthma and hay fever.

In the interpretation of vagotonic symptoms without apparent cause, two toxic factors are among the possibilities—ductless gland disturbances and chronic bacterial infection.

Two types of thyrotoxicosis are mentioned, the division following the line of physiological antagonism between the vagus and sympathetic systems. In the vagotonic cases there is present a vago-irritant toxin; in these cases there is probably a preponderant influence of the thymus.

Increased sugar tolerance is a phenomenon connected with abnormal conditions of the ductless glands. This tolerance, seen in vagotonics generally, is suggestive of a causal relation of the ductless glands to the symptom-complex vagotonia.

In the treatment of vagotonic symptoms adrenalin gives good results in urticaria and sometimes in bronchial asthma.

W. B. T.

**Histopathology of the Autonomic Nervous System in certain Somatic and Organic Nervous Diseases.** Morse (M. A.) Jour. Nerv. and Mental Dis. (N. Y.) 1916, xlv, 1.

During the past year a routine study of selected portions of the autonomic system has been made in suitable autopsies

at the Boston State Hospital. Of the ductless glands the adrenals, pituitary, thyroid, reproductive organs, and islands of Langerhans were studied.

The material included representatives of the common organic nervous diseases, some common visceral diseases, and certain unusual conditions, as pellagra and katatonic hirntod.

Two cases of pellagra: Besides prominent chronic degenerative changes in the vertebral, semilunar and enteric sympathetic ganglia, the adrenals showed marked loss of lipoid, with areas of necrosis in the cortex, and collections of lymphocytes in the medulla. The thyroids showed an excess of connective tissue, with lymphocytic infiltrations in one case.

Two cases of paresis: In neither case did the ductless glands show anything of note. Autonomic ganglia show insignificant changes.

Two cases of cerebral syphilis: In one case an adenoma of the adrenal was observed. Autonomic ganglia showed mild lymphocytic infiltration.

Four senile cases: Two senile dements showed degenerative changes of the sympathetic system, associated with sclerosis of the anterior lobe of the pituitary. Two arteriosclerotics showed little changes in the ganglia besides an increase of connective tissue. In one of these cases the adrenal cortex contained an area of necrosis, multiple hemorrhagic foci and marked lympocytic infiltrations. There was also a chronic thyroiditis.

One case of dementia precox: This patient died of pneumonia and the adrenals showed the loss of lipoid commonly found in death from acute infection. The ganglionic lesions varied at different levels.

Several other cases were reported. in no instance were the ganglia normal. However, the changes found in the ganglia did not appear to bear any relation to those of the endocrine system, most of which were minor in nature.

W. B. T.

**Cerebral Associations of Raynaud's Disease.** Norman (H. J.) Jour. Mental Soc. (Lond.) 1916, lxii, 730.

After an historical retrospect, in which the author points out that a century before Raynaud described the symptom complex which bears his name, others had reported cases of it, yet it was reserved for Raynaud in 1862 in a thesis for the Doctorate of Medicine, to give the first real generalization of the condition and to marshal the facts in an orderly way. The author cites cases published by Raynaud in which the cerebral manifestations, associated largely with the crises of pain occurring in the disease, were hysterical in character and of major type. Other cases beginning hysterically progressed

into mental enfeeblement with slow cerebration and rapid mental fatigue. Three of his (Raynaud's) cases were attended with sudden loss of consciousness and left hemiplegia. Norman doubts the true hysterical character of these cases, believing them to be due to vasomotor disturbances in previously neurotic patients. He says that the hysterical phenomena in some cases shaded gradually into true epilepsy. Other attacks of epilepsy came on after exposure to cold weather and concomitantly with local asphyxiation.

Mania and melancholia are also noted in connection with Raynaud's disease; and in cases reported by Edgerley, Ritti and Esquirol the maniacal or depressive attacks were synchronous with the characteristic types of Raynaud's disease—local syncope and asphyxia. Norman has seen several cases of dementia precox in which Raynaud's disease became established. Three cases of the disease occurred in privates in the trenches, accompanied by mental enfeeblement with delusional trends.

Aphasia in connection with Raynaud's disease is rare. Raynaud thought it was part of an hysterical condition. In one case reported by Weiss the attack was a typical one in which the patient not only had difficulty in pronouncing familiar words, but she transposed words and syllables and used wrong ones. Her lips became pale and the retinal arteries narrowed to a striking degree. Voluntary movement was not affected, and the attack subsided in 15 minutes. It was followed by another in 4 weeks. Osler reports a similar case accompanied by paralysis of the right hand and foot. This passed off in less than a day. There were recurring attacks, involving the other side, with local syncope and asphyxia. Other authors (Stockman, Simpson) report similar cases.

Ocular symptoms were also frequently seen. The disturbance in vision occurred usually when the local acroasphyxia diminished. Ophthalmoscopic examination revealed narrowing of the arteries and pulsation of the veins when the discoloration of the extremities was at a minimum. In a case of Hutchinson, there was iridoplegia, with inequality of the pupils. Many Raynaud victims have headache, especially during the local syncope. Erythromelalgia has been often confused with Raynaud's disease. The consensus of opinion today is that the former is spinal in origin, probably syringomyelic in character.

As to the cause of the phenomenon in Raynaud's disease, the symmetry of the lesions must needs lead one to look to the central nervous system. Purves Stewart suggests profound molecular changes in the sympathetic system. Levi and Raynaud believe in an emotional factor.

(In spite of the instability of the vasomotor system in this disease, with spasticity of the vessel walls and lack of

maintained tone, together with the indubitable factor of emotional shock in the pathogenesis of the disorder, none of the authors mentioned by Norman, except the latter himself, ventures an opinion as to the basic factor being found in unstable adrenals—or at least in an imbalance in the endocrinous glands.)—W. T.

**Achondroplasia in a Calf with Thymus in place of Thyroid.** Nickerson (W. S.) Jour. Lancet (Minn.) 1917, xxxvii, 7.

The "bull-dog calf" investigated was a dwarf with relatively big head, pug nose, prognathous jaw, short body and very short legs; weight 30½ pounds. Though a fairly common type of congenitally deformed monster it has been of uncertain position in our disease categories.

A comparison of the anatomic peculiarities of this dwarf with the list of fifteen essential characteristics of achondroplasia as recognized by investigators of that disease in man (Schirmer, Centbl. f. d. Grenzgeb. d. Med. u. Chir. 1907; Rankin & Mackey, Brit. Med. Jour. 1906; Fussell, J. A. M. A. 1909) reveals an agreement in twelve and a lack of agreement in those only (shape of hand and curves of spine) in which the human and bovine types are so unlike as to preclude comparison. The conclusion seems therefore justified that that form of monstrosity exemplified by the "bull-dog calf" is achondroplasia.

In an examination of the endocrine glands the facts of prime importance discovered were: the thymus was present and normal histologically; two large masses of tissue in the position of thyroid lobes were histologically typical thymus tissue and no thyroid tissue was found. In this case therefore achondroplasia is characterized by absence of thyroid and superabundance of thymus tissue.

A replacement of the parenchyma of one of the ductless glands arising in the embryo from the branchial clefts (thyroid) by that of another gland of the series (thymus) is a factor which, I believe, has not been reported hitherto in achondroplasia, and in view of what is known concerning the function of the thymus may well be a dominant etiologic factor in the production of the deformity.—W. S. N.

**Cutaneous Conditions Associated with Diseases of the Glands of Internal Secretion and Vagotonia.** Hazen (H. H.) Interstate Med. Jour. (St. Louis) 1916, xxiii, 824.

Hazen concisely and thoroughly reviews the recent literature pertaining to the relationship of cutaneous diseases and disturbances of the glands of internal secretion. He emphasizes the importance of differentiating the symptoms of vagotonia from those of true ductless gland disturbance, and observes that neurasthenics are usually sufferers from vagotonia.—L. F. W.

## EXPERIMENTAL INVESTIGATION

**ADRENIN; Effect on the Factors of Coagulation.** Grabfield (G. P.) Am. Jour. Physiol. (Balt.) 1916, xlii, 46.

The intravenous administration of adrenin in minimal doses (0.143 cc. of a 1:100,000 solution per kilo) decreases coagulation time by increasing the amount of prothrombin in the circulating blood.—T. C. B.

**THYMUS AND REPRODUCTIVE ORGANS; Direct and indirect Effect of X-rays in White Rats.** Hewer (Evelyn E.) Jour. Physiol. (Lond.) 1916, 1, 438.

From results of experiments with X-rays the author sums up under three heads: effects of irradiation on A, the thymus; B, the male gonads; C, the female gonads.

A. Direct irradiation of the thymus does not appear to determine the appearance of Hassall's corpuscles, unless the gonads are simultaneously treated.

Irradiation of the thymus only causes slight degeneration of the male gonads, and delays sexual maturity. No alteration in the female.

Irradiation of both thymus and gonads causes degeneration of the male gonads, but weak doses cause an acceleration in young animals.

Irradiation of the whole animal when very young, and with a small dose hastens sexual development in the male.

B. The general result of other workers was confirmed, namely, that irradiation of the testes determines degeneration, the degree, broadly speaking, varying with the dose of X-rays.

C. Young ova are more resistant to X-rays than older follicles; the corpora lutea become abnormally vascular, and hypertrophy of the interstitial gland is constant, and persists.

Incidentally the effect of irradiation on the adrenals and pancreas are touched upon.—T. C. B.

**THYMUS AND REPRODUCTIVE ORGANS; Structure of, in White Rats, together with Observations on the Breeding Capacity of these Animals.** Hewer (Evelyn E.) Jour. Physiol. (Lond.) 1916, 1, 434.

After discussing the histology of the thymus and the gonads, the author points out that the feeding of thymus gland delays development of the testes in young males, and cause degeneration of the testes in adults; and that all rats are sterile, although ripe spermatozoa and ripe ova might be demonstrated histologically. There were no definite changes in the thymus itself.

The author refers to a previous paper in which it has

been demonstrated by feeding experiments that there is an interrelationship between the thymus and gonads.—T. C. B.

**(SPLEEN) Le modificazioni anatomiche ed il contenuto in glicogene del fegato nei cani operati di recente di splenectomia.** Verdozzi (C.) Arch. di Fisiol. (Florence) 1916, xiv, 81.

During the 5th to 7th days succeeding splenectomy in dogs the liver increases in weight and macroscopically and microscopically presents a picture of intense stasis of the portal circulation. During this period characteristic histological lesions are observed, attributable to the interruption of the venous circulation of the liver. These lesions are present in a minor degree from 10 to 15 days after splenectomy and are almost absent in those operated from 25 to 30 days previously.

From the 10th to 30th day after splenectomy an extraordinary accumulation of glycogen is observed in the liver cells. The author infers that the spleen intervenes actively in the amylolytic function of the liver, discharging a secretion having a stimulating action on the diastatic activity of the liver.

The augmentation in the weight of the liver during the first days succeeding splenectomy is attributable to the accumulation of venous blood consequent upon the stasis of the portal circulation. The later augmentation is attributable to the accumulation of glycogen. The karyoginetic figures observed in the hepatic cells several days after splenectomy are probably the expression of a proliferative reaction to the degenerative lesions consequent upon the stasis of the circulation.—T. B. R.

**(SPLEEN) Determinations du contenu de cholesterine et de phosphore et de la résistance des globules rouges après l'extirpation de la rate.** Donati (A.) Arch. Ital. de Biol. (Turin) 1916, lxiv, 239.

Splenectomy was performed on five dogs. In each case, as previously observed by Bottazzi, the resistance of the red blood corpuscles to haemolysis by hypotonic solutions was much greater after splenectomy than before the performance of the operation.

This increase in resistance was accompanied by an increase in the total phosphorus content of the red blood corpuscles. The inorganic and organic phosphorus were not separately determined. The cholesterol content of the red blood corpuscles undergoes no change.—T. B. R.

**(PANCREAS Pancreatic Diabetes in the Dog. IV. The Influence of Pylorus Exclusion and of Gastrectomy upon the Effects of Pancreatectomy.** Murlin (J. R.) and Sweet (J. E.) Jour. Biol. Chem. 1916, xxviii, 261.

The hypothesis is advanced that the hydrochloric acid produced in the stomach and left unneutralized in the duodenum after pancreatectomy is absorbed by the portal system and poisons the liver, causing the rapid onset of the resulting diabetes in well nourished animals.

Three dogs in good nutritive condition that had the pylorus ligated at the time of pancreatectomy excreted no sugar during the first 24 hours, owing to the absence of acid in the duodenum.

Five dogs with a previous gastrectomy, upon removal of the pancreas, developed little or no glycosuria; but one other dog when given artificial digestion and kept in good nutritive condition so that a considerable amount of glycogen was probably stored following gastrectomy and previous to pancreatectomy, developed a tolerably severe diabetes, exhibiting high blood sugar, and average G:N ratio of 1.7 and an increase of 36 per cent. in heat production. The respiratory quotient of this dog and of two others previously gastrectomized was but little lower than that of ordinary starvation. Dogs with pancreas removed after gastrectomy do not exhibit the usual profound toxemia of a simple pancreatectomy.

The results of this study taken in conjunction with the results of Rona showing the extreme sensitiveness of the mechanism which accomplishes the oxidation of glucose to the concentration of hydrogen ions, and the work of Murlin and Kramer demonstrating the beneficial effect of alkali administered to totally and partially depancreatized dogs on the oxidation of glucose, suggests that the internal function of the pancreas may be closely allied to its external function and that it preserves the proper concentration of hydrogen ions in the tissues for the combustion of glucose. It is suggested that the pancreatic hormone through which this latter function is discharged may prove to be a peculiarly adapted alkali produced by the islets of Langerhans.—T. B. R.

**(THYROID) The Iodin Content of Food Materials.** Bohn (R. M.) Jour. Biol. Chem. (Balt.) 1917, xxviii, 375.

Three methods for the determination of iodin in organic matter were compared, with the result that the method proposed by Kendall was found to be by far the most accurate.

Iodin determinations were made on many feeding materials, two natural waters and several rock salts. In the majority of samples no iodin could be detected; some showed a trace of iodin to be present.

It would appear that the presence of iodin in feeding materials of vegetable origin is accidental and serves no necessary nutritive function in the plant. Further, the iodin requirements of animals must of necessity be met by the traces that occur in plant materials, waters, etc.—T. B. R.

**(PANCREAS) Preliminary Observations on the Influence of Sodium Carbonate, administered by Duodenal Tube, upon human Diabetes.** Murlin (J. R.) & Craver (L. F.) Jour. Biol. Chem. (Balt.) 1916, xxviii, 289.

Description of the effects of treatment of five cases of human diabetes by duodenal administration of sodium bicarbonate and disodium carbonate. The latter salt is preferred. The results appear to confirm the observation by Murlin and Kramer on the effect of alkali in improving sugar utilization in depancreatized dogs. The administration of alkali in the cases investigated led to diminution in the output of sugar in the urine, a gain in weight primarily due to retention of water, and a reduction in the percentage of glood sugar independently of any factor of dilution. All of the patients felt an improvement, but this improvement was objective only in two out of the five cases.

The authors believe that their results are attributable to the facilitations of the oxidation of glucose by alkalies.

T. B. R.

**(ADRENIN, PITUITRIN) Pharmacology of Uterus Masculinus.** Waddell (J. A.) Jour. Pharm. & Exper. Ther. (Balt.) 1916, ix, 171.

This paper is a report of a part of a systematic investigation of the pharmacology of the generative organs of the male. It was found that the uterus masculinus of the rabbit exhibits spontaneous rhythmic contractions when suspended in warm oxygenated Tyrode's solution. Both adrenin and pituitary extract as well as several other drugs cause an increase in tone but a decrease in amplitude of contractions. The organ reacts pharmacologically essentially like the uterus of the female. The reactions indicate that it receives both sympathetic and parasympathetic innervation.—R. G. H.

**(ADRENIN) Pharmacology of the Prostate.** Waddell (J. A.) Jour. Pharm. & Exper. Ther. (Balt.) 1916, ix, 179.

Adrenin was found to increase the tonus of prostatic muscle of rats, guinea pigs, cats, hogs and rabbits. The reactions to other drugs indicate that the prostate has both sympathetic and parasympathetic innervation. The parasympathetic fibres have the more powerful control over the organ and are much more resistant to the injurious action of drugs than are the sympathetics.—R. G. H.

**(ADRENIN) Role of Liver in Acute Polycythemia.** Lamson (P. D.) Jour. Pharm. & Exper. Ther. (Balt.) 1916, ix, 129.

This paper reports a continuation of previous researches which include a study of the effects of adrenin injections on the red blood cell count. The marked increase in the cell

count which Lamson has shown follows injections of adrenin is due to the action of the drug upon the liver. In both dogs and cats a dose of 0.5 to 1.0 mgm. per kilogram body weight injected intravenously increases the red cells about two millions per cu. mm. The increase persists about half an hour. Removal of the stomach, intestines, spleen, etc., has no influence upon the reaction. The reaction does not occur when the blood circulates only through the thorax and head, when the hepatic artery is ligated or when the portal blood is shunted by an Eck fistula directly into the vena cava. Lamson's work sugests that the polycythemia following adrenin injections may be an adaptive reaction leading to greater circulatory efficiency. The doses used were, however, relatively large. They were something over a thousand times as great as the adrenin output per minute recently determined by Stewart in anesthetized dogs. That is, Lamson injected at a single dose about as much as the animal would secrete under the conditions of Stewart's experiments in a day. To what extent the quantitative criterion is actually applicable in such cases is as yet unknown but it should be borne in mind in evaluating results of the nature reported.

R. G. H.

**MAMMARY Gland, Cyclic Changes in, Under Normal and Pathological Conditions. I. Changes in the Non-pregnant Kuinea Pig.** Loeb (L.) & Hesselberg (C.) Jour. Exper. Med. (N. Y.) 1917, xxv, 285.

This is a continuation of Loeb's extensive studies of the past ten years on the mechanism of the cyclic changes in the mammary gland, uterus and ovary. The observations reported in the present paper were made mostly on guinea pigs in which the existing period of the sexual cycle was definitely known. It was noted that in the mammary gland there occurs a cycle of changes which correspond with those of the uterus and ovary. The gland goes through a period of cell proliferation which is at its height during ovulating and heat. This primary proliferation does not occur when functional corpora lutea are present in the ovaries. After a period of quiescence on about the fifteenth day after ovulation proliferation again begins. In some cases in which the sexual period is prolonged proliferation occurs; in others, not. Two factors seem to favor proliferation in these cases: functional corpora lutea with deciduomata and imminence of heat. Extirpation of the ovaries prevents the primary mammary proliferation and probably also the secondary. In animals having "hypotypical" ovaries (usually without well-preserved corpora lutea) the mammary glands were inactive. Extirpation of the corpora lutea accelerates the primary proliferation and its associated ovulation and heat but seems to pre-

vent the secondary proliferation. The presence of well developed ovarian follicles is essential to the primary proliferation. After hysterectomy the corpora lutea were found well preserved and the mammary glands proliferating.—R. G. H.

**(GONADS) Changes in the Pregnant Guinea Pig, the Effect of Lutein Injections, and the Correlation between the Cycle of the Uterus and Ovaries and the Cycle of the Mammary Gland.** Loeb (L.) & Hesselberg (C.) Jour. Exper. Med. (N. Y.) 1917, xxv, 305.

During pregnancy mammary gland proliferation usually first begins about the 24th day. Pregnancy as well as living deciduomata and corpora lutea probably cause augmentation of the proliferation. With the initiation of active secretion mitosis in the mammary gland soon ceases. If abortion occurred during the first half of pregnancy no secretion was produced, but in two animals that aborted during the latter half secretion was noted. After castration early in pregnancy not causing abortion mammary proliferation was absent. Extirpation of the corpora lutea during pregnancy induces a new ovulation and attendant mammary proliferation. Bovine lutein extract in large doses did not produce mammary proliferation. The paper closes with a four page discussion of the significance of the foregoing results. It is not amenable to abstracting.—R. G. H.

**ADRENALIN, Comparative Study of Certain Actions of, in the Cat and Rabbit.** Githens (T. S.) Jour. Exper. Med. (N. Y.) 1917, xxv, 323.

Of technical interest. Compares the duration and extent of effects of adrenin on the pupil and blood pressure in cats and rabbits.—R. G. H.

**THYMUS, Extirpation in Guinea Pig.** Park (E. A.) Jour. Exper. Med. (N. Y.) 1917, xvx, 129.

Several investigators have reported results that indicate that the thymus has important relations with the sex glands, especially in the male. In a number of such studies the guinea pig has been used. The results have been somewhat conflicting. Park accordingly has subjected the problem to a careful renewed study. Previous work is criticised on the grounds of inadequate technique and failure to use proper controls. Careful study of serial sections through the neck region showed that the guinea pig has so much accessory thymus tissue as to render complete thymectomy impossible; earlier reports of thymectomies in this animal must be interpreted as partial only. In twelve cases Park performed thymectomies as complete as possible in young animals and kept them with controls of the same litter and sex under identical con-

ditions. (Two exceptions as to ideal controls.) No differences could be detected between the experimental animals and the controls either as to procreative activities, growth or conditions in the various endocrine glands. Thymectomy has been reported to cause rachitic changes. No such were caused in Park's series. These studies while they do not absolutely disprove the popular theory of an intimate relation between the thymus and testes do cast much doubt upon it. At the present stage of the endocrine literature such careful studies even though negative in outcome are especially valuable. It is to be hoped that many other insecurely founded statements in which the literature abounds may soon be subjected to equally rigorous investigation.—R. G. H.

**PITUITARY, Experimental Studies on the Relation of, to Renal Function.** Motzfeldt (K.) Jour. Exper. Med. (N. Y.) 1917, xxv, 153.

In view of the fact that pituitary extracts had been observed to check diuresis in cases of diabetes insipidus Motzfeldt has made an elaborate study of the relations of pituitary and other substances to kidney function. There is a somewhat extensive literature which indicates that pituitary extracts have a diuretic effect. The experiments on the subject have been made mostly, however, for short periods of time on narcotized animals. These limitations have been ignored in formulating the widely held theory that the pituitary has a normal stimulating effect upon the kidneys. Motzfeldt worked with unanesthetized animals,—mostly rabbits,—extending the observations over several hours. In most cases the animals were given water by stomach to cause diuresis. The pituitary extracts and other substances were administered usually subcutaneously, but occasionally by vein or by mouth. The urine was collected by catheter at half-hour intervals. Extracts of intermediate and posterior lobes of the pituitary were found to have a marked anti-diuretic effect; extracts of anterior lobe had a similar but much slighter effect. This effect was constant and independent of changes in blood pressure, intestinal absorption or vagus function. It was interfered with, however, by division of the sympathetic nerve supply to the kidney. Anti-diuretic effects were demonstrated also for b-imidazolylethylamine, p-oxyphenylethylamine ("sympathomimetic" substances) the drug secale cornutum, small doses of nicotine, large doses of caffein and extracts of adrenal cortex. No effect on the polyuria was caused by strychnine, morphine, adrenin, or by extracts of thyroid, thymus, pineal, pancreas or corpus luteum. In case of salt diuresis the anti-diuretics showed little effect. Motzfeldt suggests that the anti-diuretic effect is probably mediated through the sympathetic system acting upon the kid-

neys. He does not mention the other possibility that the changes may be produced in the tissues, decreasing the amount of "free water." These studies would seem to afford an excellent basis for the rational therapeutics of diabetes insipidus—R. G. H.

**PINEAL Gland, Studies.** Horrax (G.) Arch. Int. Med. (Chgo.) 1916, xvii, 607, 627.

From experimental observations on the pineal gland the author concludes that total experimental pinealectomy is possible in guinea pigs and rats. Male guinea pigs so treated show a hastened development of the sexual organs manifested by the relative increase in size and weight of both the testes and seminal vesicles compared with control animals. Histologically, the testes and seminal vesicles of these animals show a more advanced physiologic state than do the controls.

Clinical observations in three cases were noted, one of these was certified in full, the other two presented clinical pictures suggestive of pineal dysfunction. This first exhibited adiposity and macrogenitosomia, the others showed precocity of adolescence as well as overgrowth. The first case presented very marked precocious adolescence. In this case there were intracranial symptoms, and a diagnosis of tuberculous meningitis as well as xanthocromia of the spinal fluid. Autopsy revealed a struma of the pineal gland. He summarizes his article as follows:

"Extirpation of the pineal in young chickens and lower animals tends to hasten normal maturity. Tumors of the pineal gland in children occurring before the age of puberty usually give rise to a syndrome characterized by precocious adolescence. Feeding the gland substance to young animals is said to have the same effect as extirpation, but the observations are somewhat inconclusive. A report of three cases of supposed pineal tumor, one of which was certified by necropsy, is offered as a further contribution to the study of this gland."—W. B. T.

**GOITER, Metabolism Study, with Effect of Thyroid and Thymus Treatment.** Halverson (J. O.), Bergeim (O), and Hawk (P. B.) Arch. Int. Med. (Chgo.) 1916, xviii, 800.

This report is based on a study of the metabolism of nitrogen, phosphorus, sulphur, calcium and magnesium on a patient with exophthalmic goiter, with a slight hypothyroidism. The study was made in five periods of five days each, including periods of thyroid and thymus treatment.

Without treatment there was a pronounced loss of nitrogen, phosphorus and magnesium.

Thyroid medication stimulated metabolism, this stimulation continuing after treatment was stopped. Considerable

retention of all elements was brought about. Slightly better intestinal absorption of nitrogen followed this treatment, although the loss of nitrogen by the feces continued high.

The effect of thymus administration on the metabolism was not as marked as that of the thyroid but was distinct. While the gland was being administered all elements were depressed. When the administration ceased the retention was increased.

Thyroid causes diuresis. Thymus had the opposite effect. Following thyroid treatment there was a progressive decrease in urinary indican excretion.

The weight of the patient decreased on thyroid treatment. It increased following cessation of thyroid treatment and on thymus administration.—W. B. T.

**(THYROID) Results of Recent Studies on the Ductless Glands.** Cannon (W. B.) Jour. Amer. Med. Assn. (Chgo.) 1916, lxvii, 1483.

After reviewing briefly his work on the adrenal glands, especially in regard to the effect of the emotions on the glandular secretions, Cannon reports the result of electrical estimations of thyroid gland activity. With this method, he was able to show first, that the thyroid gland is subject to impulses from the cervical sympathetic; second, that the vagus nerve and pilocarpine (a stimulator of vagus endings) have no control; third, the influence of the sympathetic is not due to anemia.

Control by the sympathetic implies that adrenin may stimulate thyroid activity, and this was proven by intravenous injection of adrenin, and by stimulation of the adrenals via the autonomic system. By continuous stimulation (fusion with the phrenic) of the cervical sympathetic changes were produced which, in many respects resemble exophthalmic goiter. Hence exophthalmic goiter may be due primarily to over activity of that part of the nervous system disturbed in emotional excitement.

In conclusion, the author states that it is not unreasonable to suppose that the thyroid gland, as previously proven for the adrenal glands, has an emergency function, which would serve to increase the speed of metabolism and augment the efficiency of the adrenin secreted simultaneously.—F. C. P.

**PINEAL Gland; Composition and Physiological Activity.** Fenger (F.) Jour. Amer. Med. Assn. (Chgo.) 1916, lxvii, 1836.

Fenger collected 2344 pineal glands from full grown cattle, 1348 from adult sheep and 5062 from lambs and noted that the glands from cattle were long and fusiform and relatively small, that the sheep and lamb glands were short and plump.

He presents a table showing the average maximum and minimum weights of the various groups of glands with their loss of moisture and their petroleum-ether soluble substance. The glands from lambs contain less phosphorus than those from sheep, and these in turn less than the glands from cattle. No adrenin or iodin were found.

Pineal glands from both species show only slight contracting power on unstriped muscle, and only slight effect on the blood pressure, pulse rate, and excised heart.

In conclusion, Fenger states we cannot, with our present knowledge of physiological chemistry, accept or even consider the pineal body as an internal secretory organ of medicinal value.—F. C. P.

**(ADRENIN, etc.) Endermic Reactions.** Sollmann (T.) and Pilcher (J. D.) Jour. Pharm. & Exper. Ther. (Balto.) 1917, ix, 309.

This is an extensive research on the effects of various drugs applied to the scarified skin, amounting essentially to a study of experimental urticarias. In the research adrenin and pituitrin, among many other substances, were employed. Mulford's pituitary extract was found to produce within five minutes a marked blanching of the skin which extended somewhat beyond the scarified area and was surrounded by an area of slight reddening. There was no wheal nor any "goose-flesh" produced. The blanching persisted between ½ and 1½ hours. The effect of histamin which has been supposed by some to be the actual active substance in pituitary extract was quite different. It produced marked erythema and urticaria.

Adrenin produced marked blanching in the scarified skin of both human subjects investigated. This was true even with a solution of 1:100,000. With 1:1000 a very white area extending somewhat beyond the scratches was produced within one minute. This gradually faded away, disappearing in about 2½ hours. In one of the subjects, but not the other, the blanched area presented a striking "goose-flesh" appearance. This was due to a stimulation of the erectores pilorum muscles rather than to anemia since it was not produced by pituitary extract. Adrenin applied even to the intact skin of one of the subjects produced a marked blanching. The observations as a whole indicate that neither local vasodilation nor vasoconstriction play any essential part in producing urticaria.—R. G. H.

## CLINICAL STUDY

**(PITUITARY) A Case Bearing on the Function of the Pituitary Body.** Boyd (Wm.) Jour. Amer. Med. Assn. (Chgo.) 1917, lxviii, 111.

Boyd reviews briefly some of the theories relative to the function of the hypophysis, and reports a case of glioma of the interpeduncular space, involving the infundibulum of the pituitary body. Briefly the case exhibited the following points of interest: Boy, ten and a half years old, with the general symptoms of brain tumor, a slight enlargement of the sella (roentgenogram), very high sugar tolerance and absence of skeletal and sexual changes. Operation by Dr. Harvey Cushing, by transphenoidal route, death in a little more than three weeks. At autopsy, a glioma was found in the interpeduncular space, surrounding and constricting the infundibulum of the pituitary body. The author believes this case to furnish additional argument in favor of the theory that the secretion of the posterior lobe of the pituitary passes via the infundibular stalk into the third ventricle.—F. C. P.

**HYPERTHYROIDISM and Its Relation to Certain Pelvic Disorders.** Eastman (T. B.) Jour. Indiana St. Med. Assn. (F. Wayne) 1916, ix, 465.

Eastman calls attention to the close relationship between the thyroid gland and the genital tract in certain invertebrates, and reports two cases showing this relationship in the human race. In one case with a fibrocystic ovary associated with enlargement of the thyroid gland, removal of the ovary and tube resulted in relief from the hyperthyroidism. In the second case, one suffering with dysmenorrhea and menorrhagia, with a normal pelvis and all the typical findings of hyperthyroidism, removal of a part of the thyroid gland relieved her menstrual as well as thyroid symptoms. He concludes that there is a close interrelationship between the ovaries and thyroid. Thyroid secretion and ovarian secretion do not supplement each other, they neutralize each other.
F. C. P.

**(THYROID) Hyperthyroidosis Associated with Gynecomastia.** Freeman (J. K.) Therap. Gazette (Detroit) 1916, xl, 9.

The author reports a case of a man 37 years of age suffering with the typical symptoms of over activity of the thyroid gland, associated with an abnormal development of the mammae.—F. C. P.

**(THYMUS) Myasthenia Gravis with Thymoma.** Jones (W. A.) Jour. Amer. Med. Assn. (Chgo.) 1916, lxvii, 1354.

The author reports in detail a case of myasthenia gravis

in which at autopsy, following sudden death, a tumor about the size of a damson plum was found in the thymic region. Microscopically, the tumor consisted of fetal thymic tissue. He further calls attention to the unsatisfactory literature on this subject.—F. C. P.

**THYROID Disease in Relation to Rhinology and Laryngology.** Shurley (B. R.) Jour. Amer. Med. Assn. (Chgo.) 1916, lxvii, 1726.

This author calls attention to the physiologic and pathologic relation of the tonsils to the thyroid gland, and states that his attention has been directed to this subject by the beneficial results of a series of tonsillectomies for the relief of recurrent tonsillitis and quinsy, attended by incipient typical and atypical exophthalmic goiter. In his experience, the laryngeal muscles often show some insufficiency, varying with the size of the goiter; hyperemia of the pharyngeal, bronchial and pulmonary mucosa is common in exophthalmic goiter; if the gland is hard, it may cause tracheal cough. He believes that more rhinologists and otologists should bear in mind the close relation between the thyroid gland and the organs in their special field. —F. C. P.

**PINEAL Tumor with Invasion of Midbrain, Thalamus, Hypothalamus, and Pituitary Body.** Warren (L. F.) and Tilney (F.) Jour. Nerv. & Mental Dis. (N. Y.) 1916, xlv, 74.

A boy of eighteen years was struck on the head with the buckle of a heavy strap in April, 1915, following which injury he developed symptoms of pain in the head, projectile vomiting and drowsiness. He later developed symptoms of thirst and had difficulty in seeing and hearing. History previous to injury negative. There was great emaciation and there were marked contractures over the entire body, so that the fingers, hands and knees were flexed. Definite catatonia was present. X-ray showed sella turcica eroded at base.

The contractures may be due to pineal gland disturbance or to pressure on the tracts and the peduncle.—W. B. T.

**(PINEAL) Progressive Muscular Dystrophy as an Endocrine Disease.** Timme (W.) Arch. Int. Med. (Chgo.) 1917, xix, 79.

The author reports a somewhat atypical form of progressive muscular dystrophy, resembling Erb's infantile type, of extremely benign and slow progress. In the cases examined it has occurred as hereditary now in the fourth generation. Fourteen individuals have been disabled thus far. Five out of seven living members of this group have been examined by Roentgen ray; of these five, four show changes in the pineal gland. The evidence presented by these cases, together with that in previous similar communications, makes

probable a close relationship between progressive muscular dystrophy and disease of the pineal gland.

In the author's cases the span of life seemed above the average, his findings differing from Gower's in this respect.
W. B. T.

**PINEAL Body, Hyperplasia.** Bell (H. H.) Jour. Nerv. & Mental Dis. (N. Y.) 1916, xliv, 481.

Few lesions of the pineal body have been observed. In man the epiphysis appears as a single evagination from the roof of the diencephalon. This outgrowth branches and becomes invested with a capsule from the choroid plexus. It develops rapidly until the sixth year when involutional changes begin which last until the fourteenth year, after which no further changes are observed. These involutional changes are characterized by proliferation of connective tissue, the formation of neurological plaques which may contain cysts, and the appearance of concretions.

The cells of the pineal body do not resemble those of the organs of internal secretion. The pineal cells in young individuals are similar in number and structure to those in pineal bodies of older individuals after involution is established.

Pineal cells appear to be modified neuroglia cells.

In association with the process of involution there may be tumor-like enlargement of the pineal body characterized by proliferation of the pineal cells. In association with hyperplasia of these cells there is no functional disturbance in other organs of the body.

Two autopsies are reported in which pineal bodies were found, measuring in one case 16 mm. long, 8 mm. wide and 5 mm. long vertically; in the other, 15 mm. long and 9 mm. in its other dimensions. The first gland described was more than three times, and the second more than six times, the size of the average normal pineal body. In Case I the enlargement was due to an increase in all of the pineal elements as well as cystic formations. In Case II besides a marked hyperplasia of all the pineal elements, cysts were also present but were microscopic in size.

The symptoms which have occurred with enlargement of the pineal are headache, vomiting, optic neuritis, mental apathy and drowsiness.—W. B. T.

**(PITUITARY) Radiography of the Sella Turcica and Pituitary Body.** Johnston (G. C.) N. Y. State Jour. Med. (N. Y.) 1916, xvi, 11.

The author describes in detail the technique in taking radiographs of this region, calling attention to the desirability of making a large number of observations so as correctly to diagnose the presence of pituitary disease from the radio-

gram alone. He claims that there are changes about the pituitary rather constantly present in cases of epilepsy not attended by evidence of optical changes or other evidences of pituitary struma.

He also considers radiograms important in the diagnosis of tumors of this region, of internal hydrocephalies and of "idiopathic" epilepsy.—M. B. G.

**(PARATHYROIDS) Zwie Falle von Parathyreoideatumoren.** Schlagenhaufer (—) Munch. med. Wchnschr. 1916, lxiii, 56.

Prof. Schlagenhaufer demonstrated anatomical preparations from two cases of parathyroid tumors. The first case was that of a man of 43 years, who for the past five years had severe osteomalacic involvement of the ribs, pelvis, and bones of the extremities; also a softening of the vault and base of the skull, resembling an osteitis fibrosa. The left lower parathyroid gland was the size of a plum.

The second case was that of a woman of 62 years, who showed for the last fifteen years severe and typical osteomalacic changes. The right lower parathyroid was enlarged to the size of an almond.

In both cases the histological structure of the parathyroid showed no abnormality. He believes that the operative removal of the hyperplastic gland may improve the condition.

In discussion, Dr. Maresch reported his findings in 32 cases of osteomalacia: only three times did he find parathyroid tumors, ranging in size from an almond to a chestnut. In ten cases, the parathyroids were enlarged only relatively, and the rest of the cases (Paget's osteitis deformans and osteomalacia) showed no real tumors. These cannot always be found in severe osteomalacia. But as all other therapy is valueless in such cases, he believes that an operative removal would be advisable.

Dr. Julius Bauer remarked that not rarely does the symptom-complex of tetany appear associated with osteomalacia, which speaks for an insufficiency of the gland. Adenoma of the parathyroids is sometimes found in man without any signs of osteomalacia, as there are also cases of osteomalacia associated with functional disturbances of other ductless glands (ovary, thyroid, and possibly the hypophysis). He concludes that the pathogenetic relations of osteomalacia are extremely complicated.—L. N.

**CORPUS LUTEUM, Life Cycle and Role in Menstrual Disorders.** Novak (Emil) Jour. Amer. Med. Assn. (Chgo.) 1916, lxvii, 1285.

Novak's investigation embraces the clinical and histologic study of 137 cases from the Gynecological Department of Johns Hopkins Hospital. In 102 of these, both ovaries

had been removed, together with the uterus, so that it was possible to study the histologic picture of the endometrium side by side with the histologic variations in the removed ovaries. Only by thoroughly ransacking the latter by numerous sections could the possibility of overlooking important structures be avoided. The mere presence or absence of corpora lutea on the surface of the ovary means very little. The site of even large corpora lutea is apt to be marked by only a slight hemorrhagic discoloration on the surface. Only by cutting into the ovarian substance is the true nature of such an area revealed.

A careful study of the ovaries in this series enabled Novak to secure corpora lutea in practically all stages of development, and thus to trace the life history of the corpus luteum from beginning to end. In its earliest stages, just after rupture of the graafian follicle, it is usually a small, collapsed structure, with thin, moderately undulating walls, which are of grayish yellow hue instead of the brilliant yellow color of the later stages. For this reason the earliest stages are very inconspicuous, and are commonly overlooked. Indeed, their discovery, even with careful search, must be looked upon as in large measure accidental. With the exception of the questionable observation of Kreis in 1899, no example of such an early human corpus luteum had been described until the report of Meyer in 1911. Five such very early corpora lutea are described by Novak from his material. The clinical histories are given in full, together with the histological descriptions, illustrated by photomicrographs.

All five specimens are alike in the very important particular that in all of them the epithelial cells of the membrane granulosa are, to say the least, quite intact. This fact is of prime importance in the consideration of the origin of the lutein cells. One of the strongest arguments against the epithelial origin of these cells has been the alleged degeneration and disappearance of the membrana granulosa after the rupture of the graafian follicle. In all these five cases, however, it is well preserved, and in two of them it shows definite signs of a lutein-like transformation. Sobotta's studies indicate that, in the lower animals at least, it is from the epithelium of the granulosa that the lutein cells are derived. Novak believes that the study of his material demonstrates a similar origin in human beings. As to the time relation of these early corpora lutea to menstruation, this would indicate that ovulation occurred in the first half, or perhaps we may say the second quarter, of the intermenstrual period. Emphasis is laid, however, upon the great need of securing many more early corpora lutea, the study of which throws much more light on this problem than does that of the mature corpus luteum.

The second stage of development in the corpus, the stage of vascularization, is characterized especially by an invasion of the lutein layer by small bloodvessels from the theca interna. Some of the blood in the lutein zone is present in endothelium-lined bloodvessels, and some lies free between the cells, making its way to and into the cavity of the corpus. Even in this early stage, endothelial cells may be observed here and there pushing out into the lumen, forecasting the organization of the contents which takes place later. From a physiologic viewpoint, vascularization is important because, in addition to carrying nutriment to the lutein cells, it enables their secretion to be emptied directly into the blood stream. The further development of the corpus luteum is gradually traced to the stage of full maturity. Reference to the menstrual histories of the twenty-four cases in which mature corpora were found demonstrated that in all operation had been done at periods ranging from the eighteenth to the twenty-seventh days of the menstrual cycle, i. e., the period in which the endometrium exhibits premenstrual hypertrophy.

An interesting feature of many corpora lutea, especially near the age of maturity, is the remarkable development of the theca interna cells. They are often as well developed as the lutein cells, though of quite a different type. The contrast is very striking. The large size of these theca cells, their alveolar arrangement, the richness of their blood supply, all suggest a glandular structure and function. The name of "paralutein" cells was given to them by Pinto, who, however, credited them with no special function. With this view Novak does not agree, believing that these cells are probably concerned in the formation of one of the ovarian hormones.

After describing the retrogression of the corpus luteum, the author discusses the process of atresia folliculi. A distinction is drawn between the theca lutein cell so often found in the wall of the atretic follicle, especially during pregnancy, and the granulosa lutein cell which characterizes the corpus luteum. The so-called fibrocystic ovary to which so much pathologic importance has been ascribed, represents a marked exaggeration in the number and size of the atretic follicles. It is almost always associated with excessive menstruation. While not the cause of the latter, it, like the excessive menstruation, is to be looked upon as an evidence of ovarian hyperfunction. In other words, both the hyperfunction of the ovary and the excessive ripening of follicles which results in the fibrocystic disease, are the result of the pelvic hyperemia characterizing the inflammatory and neoplastic lesions in association with which such ovaries are commonly found.

Other subjects which are discussed are concerned with

the relation of menstruation and ovulation, as based on the study of patients before puberty, after the menopause, during lactation, during pregnancy, etc. Finally, an analysis of Novak's cases failed to reveal anything like a direct relation between the degree of lutein development in the ovary and the clinical intensity of the menstrual flow. Speaking generally, the corpus luteum from a case of excessive menstruation shows no greater development than that from a case of scanty menstruation. This does not, however, preclude the possibility of functional increase or decrease being the cause of increase or decrease in the menstrual reaction. Nor can we forget the all-important fact that even though the ovarian secretion is the immediate cause of menstruation, this function is also influenced by practically all the other endocrine glands of the body. The ovary is merely the portal through which the entire ductless gland change exerts its influence on the functions of the female generative organs.—E. N.

**(THYROID) Exophthalmic Goiter.** Mackenzie (Hector) Lancet (London) 1916, cxci, 815.

During the four years 1911-1914 the number of deaths returned in England and Wales as resulting from exophthalmic goiter was 1,558 for females and 155 for males, a proportion of ten females to one male. The number of deaths increase in each five-year age-period up to 35-40. The author states that the disease is very rare in childhood, that he has yet to see a typical case under the age of twelve.

The disease shows a tendency to show itself in several members of the same family. In thirty-four private cases, other members of the family were afflicted besides the patient examined. In at least one-third of the cases the onset of the disease was preceded by some more or less severe mental shock, strain, worry or anxiety. As a rule, the symptoms of the disease develop gradually after the shock or strain, but in some cases the symptoms very quickly follow the mental disturbance.

The effect of profound emotional disturbances, such as sorrow, grief, anxiety and fear, is to produce exophthalmic goiter. The author considers fright to be a short attack of exophthalmic goiter.

From what is known of the causation of the diseaes, prevention is out of the question. Persons in whom there is a family history of the disease should steer clear of occupations involving more than the ordinary responsibility, worry or anxiety.

In the thirty-six post mortem examinations held on cases of exophthalmic goiter at St. Thomas' Hospital, the most constant feature next to the thyroid enlargement was the presence of a persistent or enlarged thymus gland. In three

of the fatal cases the duration of the disease was less than six months; in ten, less than one year; in twelve, less than two years; in eight, less than six years; and in six, over six years. In more than half of the cases it was less than eighteen months.

The blood picture of exophthalmic goiter is that of any disease of the endocrine system, namely, a white cell leucopoenia with a relative lymphocytosis.

The hypodermic injection of the extract of the posterior lobe of the hypophysis slows the pulse in patients suffering from exophthalmic goiter. The instillation of adrenalin into the conjunctiva causes dilation of the pupil in goiter, and also diabetes. Exposure of the thyroid and thymus glands to the X-ray is the best means of treatment. It must be continued for a long time. The early cases are the ones most benefited by this treatment.

The author's experiences with the operative treatment of the disease have been unfavorable. If operated at all, local anesthesia should be used. Ligature of the thyroid arteries is not very effective. If possible, it is best to remove more than one lobe, otherwise it is probable that another operation will be necessary.—W. B. T.

**(PANCREAS) Del diabete neurogeno.** Silvestri (T.) Rif. Medica (Naples) 1916, xxxii, 281.

In an interesting study of the possible neurogenic origin of diabetes mellitus Silvestri reports the clinical course and autopsy findings in a case of diabetes in which there were no pathologic anatomic findings capable of explaining the diabetes. This author presumes that it was of nervous origin, as the neurasthenic man of 53 had a family history of much nervous and mental disease. The literature on the subject of diabetes developing after disastrous speculation or other nervous shock is reviewed, and authors cited for and against the assumption that diabetes can be brought on by nervous factors alone.

Four other cases in the practice of this writer also apparently confirm this beyond question. One patient was a neurasthenic man with inherited psychopathic taint whose urine was found to contain sugar after a period of much worry. The urine after a medical examination always contained sugar. In the course of a few years the neurasthenia subsided, and the urine became normal. At present there is no further trace of the neurogenous "diabetes" of eight years before, although no attempt at dietetic treatment had been made. Another patient was a woman with a family history of diabetes. After an attack of pneumonia she had mild glycosuria which yielded promptly to restriction of carbohydrates until her son developed typical diabetes which ran its course to a

fatal ending in three years. After this the mother's glycosuria became permanent, unmodified by dietetic measures. In the two other cases the glycosuria came on directly after a severe grief or fright.

These experiences testify that diabetes may occur for the first time or be roused or aggravated by nervous shocks, and Silvestri explains the probable mechanism by which this is brought about. He has been unable to trace it to any one gland or other organ, but the influence of a hereditary taint seems to be obvious.

**OVARIAN Transplantation, with Report of Cases.** Phillips (W. D.) Texas State Jour. Med. (Ft. Worth) 1916, xii, 213-16.

The author reviews the history of ovarian transplantation, and reports the results of twelve cases of autogenous ovarian transplantation which he has observed with Dr. C. Jeff Miller, since Dec., 1914. Phillips used grafts varying in thickness from one-sixteenth to one-eighth of an inch, and always sectioned the transplant from the healthiest portion of the ovary. One or more grafts were imbedded in each case. In seven cases the transplant was placed in the adipose tissue of the abdominal wall resting on the rectus sheath; in the remaining five cases it was embedded underneath the rectus muscle, resting on the peritoneum. No sutures were used to retain the grafts in place. In three cases the graft was alive and functioning two years after operation. Of the twelve cases, six are menstruating regularly, while the remaining six could not be reached by letter. The writer is convinced that the operation is without danger and its use will not only diminish the cases of precipitated menopause, but will also lessen the indications for second and even third laparotomies.

L. F. W.

**(ADRENIN) Correlations between the Systolic Blood Pressure and Refex Vasoconstriction (Anemic Dermography).** Tracy (E. A.) Boston Med. & Surg. Jour. 1917, clxxvi, 15.

In a previous paper it was shown that anemic dermography is caused by stimuli coming over the sympathetic fibers, together with adrenin in the blood stream. The present paper is based on a study of 125 cases in which the systolic blood pressure was noted and at the same time the time valuation of anemic dermography was taken, on analysis of the data obtained two correlations were disclosed: (1) Low reflex vasoconstriction valuation was accompanied by or correlated with low blood pressure. (2) High blood pressure was correlated with high reflex vasoconstriction valuation.

These correlations are highly suggestive when we recall that German clinicians correlate hypertonicity with hyper-

plasia of the chromaffin tissue (which secretes adrenin), and that Addison's disease is associated with low blood pressure. The question at once arises, is there any relation between reflex vasoconstriction and the adrenin content in the blood? Experiment and reasoning lead the author to believe that the relation between them may be expressed briefly thus: reflex vasoconstriction—anemic dermography—measures comparatively the adrenin content in the blood stream.—E. A. T.

**PITUITARY Fossa, Accurate Radiography of, and of the Sphenoidal Sinuses.** George (H. T.) Arch. Radiol. & Electrotherap. (Lond.) 1916, xxi, 169.

The author reminds us of the importance of accuracy in the Roentgenography of the pituitary fossa and for the purpose of bringing the saggital plane of the skull parallel with the plate, he places a ring of metal in the proximal ear and a smaller disc in the opposite ear and then centralizes them fluoroscopically.

This he considers an improvement over Finzi's method of using a coin for this purpose. Having obtained these parallel planes the author passes the central ray through the skull at a point 3 cm. in front of the external auditory meatus, and 2½ cm. below the line connecting the external auditory meatus and the external canthus. This should give an accurate outline of the sella turcica.—G. E. P.

**[Growth Anomalies in Women.]** Schiötz (C). Norsk Magaz. f. laegevidensk. 1916, lxxvii, 909.

The author has studied the anthropological proportions in two cases of apparent infantilism. Contrary to the conditions in "true" infantilism there was an abnormal length of the extremities—more like the conditions in eunuchoidism.

Case I. Girl, 18 years old, 137 cm. high, weight 33 kg No secondary sex characteristics. Arms and legs unusually long, as compared with the normal conditions. Bitemporal narrowing of the field of vision. High carbohydrate tolerance. The condition is chiefly due to insufficiency of the anterior lobe of the pituitary body and also of the ovaries.

Case II. Woman, 30 years old, 171 cm. high. Amenorrhea. Atropic uterus. Abnormal length of the extremities. No development of mammae. Very much like the castrate type. Primary insufficiency of the ovaries (?).—K. M.

**[PITUITARY Tumors.]** Schiötz (C.) Med. Revue. (Bergen) 1916, xxxiii, 91.

Case I. Man, 36 years old. Clinical diagnosis: tumor of the hypophysis and adipositas,—without other manifestations of dystrophia adiposo-genitalis. The autopsy revealed an adenoma of the pituitary body. Microscopic examination of

the other ductless glands showed: Colloidal struma of the thyroid, an unusual amount of fat in the parathyroids, and an augmentation of connective tissue in testes, with absence of Leydig's cells.

Case II. Man, 50 years old. The clinical manifestations, hemorrhagic pleurisy, hemiparesis and polyuria (3500 mils.) were considered due to metastases from a malignant new-growth. Roentgenogram showed destruction of the sella turcica. Autopsy: Carcinoma of the lung, pleurae, brain and the pituitary body. The anterior lobe was not involved, but there was a complete destruction of the pars intermedia and posterior lobe.—K. M.

**Internal Secretions and Eye Diseases.** Schirmer (O.) N. Y. State Jour. Med. (N. Y.) 1917, xvii, 1.

The author deals with the ocular manifestation of abnormal functioning of the glands of internal secretion.

He believes that all diseases of the eye due to hypophyseal or pineal gland trouble are the result not of the internal secretions of these glands but of direct pressure due to their enlargement.

He does not believe that the exophthalmos in Graves' disease can be explained by a continuous contraction of the non-striated muscular system in the orbit, but he assumes that at an early stage a swelling or even an hypertrophy of the fat tissue develops and keeps the eyeball protruded. This would account for the fact that in cases completely cured by surgical interference, all the Basedowian symptoms disappear whereas the exophthalmos frequently remains.

He calls attention to von Hippel's results in using the Aberhalden method for ascertaining the condition of the endocrine glands in eye diseases. Keratoconus is the one eye disease giving positive results by this method, using thymus and thyroid, frequently with both of them; sometimes the adrenals, the pancreas or the gonads give a positive reaction, indicating that in this disease the endocrine functions are disordered. The pathological changes must be slight as none of the well-known endocrine diseases have been observed in these cases.—M. B. G.

**AKROMEGALIE, Beitrag zur Klinik und Therapie.** Fürth (C.) Med. Klin. (Berl.) 1915, xi, 1347.

A case is reported which is of interest because ten years' observation showed certain peculiarities which may throw a light on the pathogenesis of acromegaly, its prognosis and the value of a therapeutic agency.

The patient, a woman forty years old at the time of first observation, had a typical appearance of acromegaly. Her father had a goiter and died at the age of 62, showing a rapid

disappearance of the goiter and a rapid physical and mental decline; family history otherwise negative. She was a healthy child menstruated at 14, married at 22, but never became pregnant. Toward the close of the second decade, the menses decreased in amount and frequency, and stopped entirely at 33. At this time the manifestations of acromegaly set in, the face becoming larger, especially the nose, chin, lips and tongue, and the teeth became separated. The hands and feet became more plump, and the skin of the chest and back grew short, stiff hairs. Light attacks of dizziness were the only subjective symptoms. For seven years the bodily measurements steadily increased so that finally the acromegaly was typical.

Then visual disturbances set in which were promptly improved by administration of iodides, and after one month of treatment the visual field became practically normal. Later the eyesight again became weaker.

The ophthalmological findings indicate that various disturbances of the visual field may be found in tumor of the hypophysis; secondly, that wide excursions of the visual disturbances may occur at short intervals; and thirdly, that therefore the prognosis of the visual disturbances, as well as the judgment of therapeutic results, must be given with caution.

In regard to therapeutics, the author cannot say much. Sodium iodide, at the time of the first visual disturbances, caused improvement and was continued. The patient felt so much improved, that she asked to have it continued. The dose had to be gradually increased, so that after three years she was taking 114 grams a month, and after five years 210 grams. The therapeutic effect of this dose was then lost, and the patient reacted only to such large doses as 8 and even 14 grams per day. For weekly periods she also took thyroidin, which was well borne.

At the beginning of treatment, for about one year (on and off), five tablets of ovarian extract were given daily, and later for several years, three tablets of hypophyseal extract were given daily. These organic extracts, however, had absolutely no effect on the visual disturbances, whereas the iodide had a distinctly ameliorating, or at least a retarding, effect. After five years even this effect wore off, and despite the large dosage, vision gradually became poorer.

How is the patient's reaction to iodide to be explained? The radiogram proved the presence of a tumor of the hypophysis, also the destruction of the sella turcica, as well as the dorsum sellae and posterior clinoid processes, whereas the anterior clinoid processes and the anterior half of the pituitary fossa remained untouched. The influence of iodides on various neoplasms is well known, and perhaps the inhibit-

ing effect on tumors is not seen more often because of a too small dosage. In this case, enormous doses were tolerated, and this may have caused the regression of the tumor. However, the unusual tolerance in this case would speak for a specific effect.

According to the current views on acromegaly (Biedl, Pineles), the etiology is not only a disordered function of the hypophysis, but also that of the other ductless glands as well, and it would be nothing unusual for their iodin content to be disturbed. Palpation of the thyroid was negative. It is reasonable to believe that the power of absorbing large quantities of iodide was due to the diminution of the endogenous production of iodin, and that the otherwise toxic effects of this diminished iodin production were held in abeyance by the giving of sodium iodide.—L. N.

**(PITUITARY) Ueber familiäre Akromegalie.** Leva (J.) Med. Klin. (Berl.) 1915, xi, 1266.

Leva maintains that in spite of animal experimentation and pathologico-anatomical investigations, the etiology and pathogenesis of this disease are still obscure. Acromegaly may appear at any age, although it has a predilection for the young. As exciting causes are given trauma, emotional disturbances, infections, pregnancy and plumbism; in addition, a hereditary family predisposition is claimed by some to play a definite part.

With special regard to the last mentioned cause, the author reports two cases. The patients were first cousins, one 28 years old, an assistant builder, the other 26 years old, a priest. They grew up in different surroundings and had no personal dealings with each other. Five years ago, both noticed that their fingers and toes gradually became thickened at their outer ends, and also progressively deepening folds appeared in the skin of the occipital region, and finally also the skin of the forehead and face. The skin condition has become more marked the past year, and there has developed a remarkable resemblance between the two patients never noticed before, which has resulted in their being mistaken one for the other.

The similarity of progress of the two cases and their family relationship prompted the author to investigate their family antecedents. Not only were the two patients the sons of two sisters, but a consanguinity was established, inasmuch as the grandfathers descended from a brother and sister of the same family as the mothers.

Previous studies of the causes of acromegaly rest upon anatomical and physiological studies. Pierre Marie claimed that this disease was caused by a neoplasm of the hypophysis. On the other hand, other authors assert that in many cases

of acromegaly no tumor was found, and again in other cases, hypophyseal tumors did not develop symptoms of acromegaly. This contradiction was only apparent: the neoplasms were often only microscopically visible, or they developed first in the vicinity of the hypophysis, escaping detection. Often the tumor was a simple adenoma or an hypertrophy of the hypophysis.

By means of extirpation experiments proof was brought by Biedl, Cushing, Aschner and others that the hypophysis may be divided into three parts according to their physiological importance: an anterior lobe, the pituitary gland, and the posterior lobe (neurohypophysis). The anterior lobe is the most important, and its extirpation leads to apituitarism and death. Partial extirpation of the anterior lobe results in obesity, polyuria, glycosuria, loss of hair, impotence, and atrophy of the testicles and ovaries.

Aschner proved that extirpation of the hypophysis in adult animals caused only minor changes of nutrition with a lowering of general resistance. Young animals showed greater changes, e. g., inhibited growth, loss of muscular power, obesity, separation of the epiphyses, colloid increase in the thyroid, and hypoplasia and atrophy of the genitals. The younger the animal, the greater was the disturbance.

It was demonstrated that functional disturbances of the hypophysis resulted in marked bodily changes, especially in growth and metabolism, and acromegaly was proved to result from hyperpituitarism.

Some authors claim hereditary neuropathic tendencies associated with consanguinity as an etiological factor of acromegaly; and de Cyon reports three cases in three sisters of one family. Schwoner reports a case of a woman of 50 years whose mother also had acromegaly, and was also 50 years old when it developed; the course of the disease in both mother and daughter was the same. In this case it was remarkable that all the members of this family, both on the mother's and father's side, grew to an extraordinary height.

Other observers noticed this fact and the question arose as to what relationship there was between acromegaly and gigantism. Klebs considered gigantism and acromegaly as the same disease. He believed the hypertrophied hypophysis is a constant accompaniment of gigantism. Gigantism could manifest itself as a simple increased physiological growth, or as a disease (acromegaly). He could not see an etiological relationship between hypophyseal hypertrophy and gigantism.

Virchow and Pierre Marie dissented from this view. Marie believed in a complete dissociation of gigantism and acromegaly. In his opinion, gigantism was a physiological process, whereas acromegaly was pathological.

To-day even this view is obsolete. Sternberg showed

that one-fifth of acromegalics are giants, and that a half of all giants are acromegalic. An intimate relation between gigantism and acromegaly cannot be proved; and although gigantism does not result from acromegaly, nevertheless, there is evidence that gigantism frequently accompanies acromegaly—it forms a predisposition to acromegaly. There is sufficient ground for the belief that certain constitutional causes can lead to the development of acromegaly.

Both of the author's cases show no signs of gigantism. Nevertheless in these cases, as in acromegalic giants, the etiology of this disease cannot be ascribed to a well defined change of the hypophysis. The similarity of the course and symptoms, and especially the results of the genealogical investigation bespeak for the fact that a constitutional substratum, plus the possibly cumulative effect of a neuropathic tendency, led to the development of acromegaly in the reported cases.—L. N.

**(THYROID) Hyperthyreoidismus bei Kriegsteilnehmern, neurogenen Entstehung dieser Krankheit.** Rothacker (A.) Münch. med. Wchnschr. 1916, lxiii, 99.

Opinions as to the origin of Basedow's disease may be divided into two classes: the thyrogenous, as advanced by Moebius, and the neurogenous, as promulgated by Oswald.

The research on enzymes as conducted by the pupils of Abderhalden points to the former theory. They have concluded that Basedow's disease means not only a disordered function of the thyroid, but also that of the thymus and generative glands, inasmuch as goitrous serum strongly affects an exophthalmic goiter, and in relatively few cases even the normal or hypertrophied thyroid. At the same time there is a distinct atrophy of the thymus and generative glands. Lampe believes that hyperthyroidism involves the branchiogenic organs in their entirety. The author believes that it would be desirable to investigate the effect of goiterous serum on the nerve substance, and also to determine which organs would be affected by this serum in "nervous" or neuropathic individuals.

The majority of investigators to-day believe in the theory of Moebius. A close study of the histories of some cases of Basedow's disease will undoubtedly lead to the conclusion that this condition is of nervous origin. Oswald lays stress on the fact that all persons do not respond to a hyper-secreting thyroid with symptoms of Basedow's disease; a predisposition to this disease is necessary, and the genetic factor lies in the nervous system. It is in this manner that the thyroid secretion causes Basedow's disease in persons with an impaired nervous system. Mental strain or continuous excitement is an exciting cause. The primary cause is a

weakened nervous system (of no direct connection with the thyroid), and the struma is a secondary symptom resulting from the thyroid secretion. The thyroid receives its impulse from the nervous system of which it is physiologically a part and acts through a specific substance as an intensifier.

The author then gives histories of three patients in civil life, which show as the result of fatigue and overexertion, and mental excitement, not only a remarkable thyroid enlargement, but also typical Basedow's disease. The pathological manifestations receded immediately the disturbing elements were removed and the patients returned to their normal conditions.

Rothacker then cites three cases from military life, which showed an acutely developing Basedow's disease caused by the nerve concussion, the excitement of machine-gun fire and trench warfare. After a rest of several months all three cases made an uneventful recovery.

Many similar cases were seen by the author. These were often at first considered as "heart disease," but a close study of their histories reveals typical "acute Basedow's disease." These subjects are unfit for field service in modern warfare, as the exhausting long marches in water-soaked districts, the continuous fighting, and the forced marches by night and day caused overacting hearts, slight rises of blood pressure and "nervousness." Neither enlargement of the thyroid nor exophthalmos could be observed after exertions of short duration. It is noteworthy that many soldiers informed the author that at the time of greatest excitement in the field they had more frequent desire to urinate and daily polyuria as compared with peace times. Injury to the hypophysis may be excluded. Such conditions are known to happen in nervous states, but nothing definite is known of the cause.

The author cites these cases to support the theory that many cases of Basedow's disease are of nervous origin, and especially in these cases of soldiers, who develop these symptoms after great mental excitement, and return to normal as soon as the offending cause is removed. This proves, to the author at least, that these cases are of nervous and not of thyroid origin.

As a related subject, Rothacker recalled certain experiments of Abderhalden. He found that the serum from nervous or neuropathic patients, and also those with enlarged spleens of different origins (typhoid, cirrhosis of the liver, leucemia, etc.) almost always decreased the size of the normal spleen and lymph glands, and the thymus always. These patients showed no signs of Basedow's disease. He suggests that Abderhalden's experiments be used to investigate the origin of Basedow's disease.—L. N.

## THERAPEUTIC EXPERIENCES

**OVARIAN Extract, Therapeutic Application.** Morley (W. H.) Jour. Mich. State Med. Soc. (Grand Rapids) 1916, xv, 372.

After describing briefly the anatomy and physiology of the ovary, Morley emphasizes the fact that the three divisions of the ovary, i. e., the follicular apparatus, the corpus luteum, and the interstitial gland, do not have their functions sharply defined, the one from the other. At times they all work in perfect harmony in carrying out the internal secretory power of the ovary. Exact histological studies have shown that menstruation and ovulation do not occur synchronously, as was formerly supposed, but that ovulation occurs in the interval, ten days before the menses are ushered in. Up to recent times, the ovary has failed to yield the active principle of its internal secretion. Morley states that practically no results have been obtained therapeutically except with the desiccated product. During the last year a water soluble powder was obtained from the corpus luteum. The most common indication for the use of ovarian extract is furnished by the troublesome symptoms of the menopause, such as flashes of heat or cold, insomnia, nervousness, etc. It is surprising what relief may be given by the use of desiccated corpus luteum, properly administered. One great advantage in this medication is that it does no harm if no relief is accomplished. As far as can be learned from the use of the soluble product, relief may be obtained in less time and with fewer doses, and it will be more permanent than with the dried gland. Perhaps the action of the gatsric juice has some effect upon the efficiency of the product. At all events it is always better to use the active principle, where it can be obtained, than to trust to the action of the entire gland with its varying amount of inert substances. Morley also states that the use of either the desiccated product or of the soluble extract is often productive of good results in amenorrhea or in scanty menstruation. He believes that the failure to obtain good results in many cases in which the entire gland is given may be explained by the results of Seitz, who found that the corpora lutea of beef ovaries contain two antagonistic bodies which he called luteo-lipoid and lipamin. The former of these substances was found, when subcutaneously injected, to lessen the flow and shorten it. The second, lipamin, caused an increased growth of the internal and external genitalia in animals, while in women, by subcutaneous injection, it will cause the menses to appear in amenorrhea. In the young corpus luteum there is more lipamin, and the flow appears. Later

the luteo-lipoid has the upper hand, and the menses stop. This goes to show that until the active principles of the ovary are isolated beyond peradventure of a doubt, its therapeutic use will be more or less problematical.—E. N.

**(GRAVES' DISEASE) Disease and Electrical Treatment.** Hernaman-Johnson (F.) Lancet (Lond.) 1916, ii, 920.

The X-ray is most efficient in the treatment of Graves' disease. The best results follow the application of the ray at frequent intervals, not less than three times a week in mild cases; in acute cases, daily. Hard rays, filtered through aluminum, should be used. Pain, anxiety, fatigue, constipation and dental trouble are given as possible causes of failure.

A portable apparatus may be carried into a private house if the patient is acutely ill; bedside applications of the ray in the early stages of acute exophthalmic goiter would save many lives.—W. B. T.

**(PITUITARY) Ueber die Wirkung des Hypophysenextracts bei Thyreosen.** Pal (J.) Deut. med. Wchnschr. (Berl.) 1915, xli, 1537.

The extract of the infundibular portion of the hypophysis (pituitrin, pituglandol, etc.) produces effects on hyperthyroidism or Basedow's disease of no mean therapeutic value. Prof. Pal's experiments were based on the use of pituitrin, to which he was led by the contradictory results of pituitrin and thyroid extract upon the arteries. It is still a moot question whether substances like pituitrin, pituglandol, or glanduitrin circulate as such in the blood and have any effect.

The extract of the infundibular portion of the hypophysis was used in 16 cases of Basedow's disease and hyperthyroidism; different reactions were observed. At first 15 to 30 minims were given. Although remarkable results were obtained, subcutaneous injections were given instead. The author's interest was then attracted to the cases of cachexia with low blood pressure and signs of severe intoxication.

Of nine unoperated patients, seven gained in weight and improved subjectively and objectively, showing abatement of the restlessness, tremor, and sweating. The exophthalmos was improved very little or not at all. Tachycardia was only slightly improved, to return when treatment ceased. The most noteworthy effect was that the patients felt so much improved subjectively, that they requested that the resumption of the treatment whenever it was discontinued.

Three case histories of Basedow's disease are presented. Each was in such a reduced condition that an operation was inadvisable, and treatment with hypophyseal extract was tried. They improved but the thyroid became enlarged simul-

taneously, and later resections were done. In two cases the structure of the thyroid seemed to change with the decrease of the pulse frequency. The histological picture leads to the belief that the pituitrin injections inhibit the hypersecretion of the thyroid into the blood, and also that they do not prevent the escape of the secretion from the follicle, but even favor it, so that at the expense of the follicle the thyroid enlarges. This seems to be contrary to the findings in healthy animals.

In human beings with apparently normal thyroids, in whom pituitrin, pituglandol, glanduitrin or hypophysin were injected experimentally for cachexia or malnutrition of different origins (tuberculous, gastric or nervous disorders), no appreciable influence on the structure of the thyroid could be traced, although an occasional beneficial effect was seen on the nutrition. However, this may be due to the tonic influences of the pituitrin on the smooth muscle of the digestive tract. The influence on gastric secretion might also be considered, but nothing positive was noted.

It must also be mentioned that no effect was noticed on the normal or hypertrophied thyroid. The change is noticed only in those cases where the internal secretion is disturbed, especially in Basedow's disease during an exacerbation, and in hyperthyroidism. In the latter group, pituitrin gave most remarkable results, as was shown by a reported case of thyroid atrophy with symptoms of hyperthyroidism (intoxication). A few injections of pituitrin not only relieved the severer symptoms but, also, in a few days caused a visible increase of growth in the previously completely atrophied thyroid. It saved an almost hopeless life as if by magic. This teaches us that subcutaneous injections of pituitrin can arrest an atrophy of the thyroid associated with hypersecretion.

The rapid relief from thyreotoxic symptoms leads to the belief that the thyroid secretion is in some way inhibited or decreased by the pituitrin; at least it may be influenced in such a way that the secretion does not reach the circulation in the same amount as before. It must also be observed that the thyroid grew in size with the formation of nodules. We must conclude that there was an increased follicular secretion, and this explains the fact that the formation of colloid and the secretion of thyreotoxin has two opposite functions in the circulation. It should also be noted that the extract of the infundibular portion of the hypophysis has an inhibitory effect upon the irritated glandular epithelium of the thyroid.

The author claims that his experiments explain the beneficial effects of hypophyseal extract in Basedow's disease, and that it is due to an abatement or arrest of the symptoms of thyroid intoxication. A complete disappearance of the symp-

toms in pronounced cases of Basedow's disease was not observed. This form of treatment did not work as well in other cases, where, as in one case, 20 drops by mouth and one injection had no effect, and in another chronic case the improvement was relatively slight.

Another case of Basedow's disease following iodin therapy, was that of a man with arteriosclerosis. He improved under pituitrin, but the injections were discontinued after the appearance of arterial spasms, resulting in gangrene and ending in death from myocarditis. The author believes that the arterial disease was aggravated by the treatment, as in these conditions symptoms of hyperthyroidism usually supervene, and, therefore, he counsels caution in the use of pituitrin in these cases.

Occasionally increased blood pressure has resulted from the subcutaneous injections of pituitrin, but no ill effects were observed. The treatment of hyperthyroidism with pituitrin must be governed by the individual reaction, as effects have been observed from 0.2 to 0.3 gram of the dried hypophyseal extract in one case, which could be equalled in others only by very much larger doses.—L. N.

**PITUITARY; Ueber Kachexia hypophysaren Ursprungs.** Simmonds (M.) Deut. med. Wchenschr. (Berl.) 1916, xlii, 190.

Simmonds reports a case, similar to the one he reported two years ago: A shoemaker, of negative past history, has steadily become weaker, thinner, and pale for the past two years. He constantly felt cold and finally had to discontinue his work. Despite careful and frequent examinations, no organic disease could be discovered. The blood count showed hemoglobin 60 per cent., erythrocytes numbered 3,500,000, and leucocytes 4,600. The differential count was lymphocytes 47 per cent., polynuclears 48 per cent., and eosinophiles 5 per cent. The temperature showed an occasional twenty-four hour rise. For months this was the only finding, and as the cachexia constantly increased, the diagnosis of a cryptic carcinoma was made. Only the eight days preceding death, caused by pneumonia, showed a continuous rise of temperature.

The autopsy findings were disappointing. Outside of the pneumonia and pericarditis, nothing abnormal was found in the chest and abdomen. The liver was enlarged, and the bone marrow and heart muscle were negative for pernicious anemia. The head, however, showed the seat of trouble. On removing the brain, there was noticed a tumor, the size of half a hazelnut, grayish white in color, corresponding to the hypophysis; separated from it by the sella turcica was an equally large second tumor, taking the place of the hypo-

physis. The sella turcica was much enlarged, smooth, and the optic nerves were displaced by the mass. Between the two masses (resembling an hour-glass) no recognizable remains of the hypophysis were seen. Microscopically the tumor proved to be an adenoma.

Although this was a benign tumor, nevertheless, by its encroaching size, it destroyed the hypophysis, and produced cachexia. The tumor did not cause acromegaly because of its basophilic character. The testicles and prostate, however, were distinctly atrophic, and the hair of the face and public region were very thin, but otherwise distinctly masculine characteristics were retained.

The second case cited by the author was that of a girl, 9 years old, with a histoy, autopsy and microscopical findings practically identical with the first case.

The remarkable fact of the three cases was the extremely severe chronic cachexia ending fatally, for which the most painstaking study showed no explanation. The only pathological finding of the three cases was a total destruction of the hypophysis, twice from a neoplasm, and once from an old embolus. Therefore it is assumed that the cachexia followed the destruction of the hypophysis, and the resulting absence of its secretion. This has not been previously noted, because there are so many complicating symptoms and diseases to this affection of the hypophysis, that the cachexia was either overlooked, or at least was not considered seriously enough, nor emphasized. The true relationship can only be seen in cases where there are no veiling circumstances. In fact, the cachexia appears only after total destruction of the hypophysis, and as long as only a part of it is left, the symptoms due to the loss of the secretion will not appear. The same rule holds as in the other organs of internal secretion.

If the author's premises are correct, that there is a cachexia due to the absence of the hypophyseal internal secretion, then follows the conclusion, that in all cases of cachexia of unknown origin, the administration of hypophyseal extract is indicated as a therapeutic trial.—L. N.

**(PITUITARY) Ueber die Beziehung des Diabetes insipidus zur Hypophyse und seine Behandluing mit Hypophysenextract.** Hoppe-Seyler (G.) Münch. med. Wchnschr. 1915, lxii, 1633.

The author cites a case history with elaborate charts, showing the effect of pituitrin on the quantity of urine passed, the amount of fluids ingested, the specific gravity of the urine, and the percentage of its salts.

The picture is undoubtedly one of diabetes insipidus; other conditions with which this disease might be confounded

are ruled out. Polyuria from the excessive ingestion of fluids is differentiated by the specific gravity remaining low independently of the amount of food and drink taken. The oliguria resulting from atropine administration is demonstrated to be due to the fluid collecting in the body (shown by the weight of the patient on the chart). This proves that the polyuria is controlled by the vasomotor nervous system, and not by the disturbed kidney cells. Of course, rise of blood pressure and hypertrophy of the left side of the heart are absent.

The condition is analogous to polyurias observed in disturbances of the central nervous system, as irritation of the floor of the fourth ventricle. A tumor or chronic meningitis (cerebrospinal syphilis) was ruled out because of the negative Wassermann reactions of the blood and spinal fluid.

The following signs pointed to involvement of the hypophysis: Marked panniculus adiposus, loss of sexual power, loss of hair, and a remarkably prompt reaction to even such small doses of pituitrin as 0.25 gram resulting in a normal excretion of urine, sweat, and saliva, which were subnormal before the injections. It might be claimed that the resulting increased eliminative powers of the kidneys cannot be used as a diagnostic measure, as such an effect can also be observed in healthy persons, and even in certain chronic nephritics. In the latter cases, however, this phenomenon was not so marked. At any rate, there is never such a rapid rise of the specific gravity and salts as there was in this case. Besides, the general well-being, the saliva and sweat, and the appetite were so much improved by the very small dose of pituitrin, that an observer must admit that just that little pituitrin was missing to restore normal conditions. As the internal secretion was absent, and as it is elaborated by the hypophysis, the author believes that an insufficiency of that gland is the underlying cause, and that all signs point against the opinion that diabetes insipidus is due to an irritation of the gland, resulting in hyperfuncton.

Nothing can be said as regards the nature of the hypophyseal changes. The X-ray shows the sella turcica plainly, with no modification in size or any other change. In regard to a chronic inflammation with increased connective tissue, nothing is noted, and signs of lues and tuberculosis are absent.

As to the therapy, it is well known that by limiting the ingestion of salt and fluids, we can decrease diuresis and the excretion of metabolic products. This was avoided in the treatment of this case. Pituitrin by mouth gave no results, nor did pituglandol, both internally and subcutaneously.

The author claims, therefore, that subcutaneous injections of pituitrin have a curative effect on diabetes insipidus, acting like thyroid extract in myxedema. He believes the

effect of pituitrin to be due to the compensation that is established by supplying the internal secretion which is wanting in this disease, and that diabetes insipidus should be considered as the result of an insufficient function of the hypophysis.

L. N.

**(PITUITARY) Ueber die Beziehung des Diabetes insipidus zur Hypophyse und seine Behandlung mit Hypophysenextract. (cont.)** Hoppe-Seyler (G.) Münch. med. Wchnschr, 1916, lxiii, 47.

In the confirmation of his previous remarks on this subject (see item commencing on page 265 of this issue), the author mentions some of the references to the literature on this subject outlining the essentials of these reports:

As a result of pathological, anatomical, and experimental observations, Magnus and Schafer concluded that there was a hyperfunction of the hypophysis in this condition. Romer showed by animal experimentation, and by a clinical study of a case of diabetes insipidus resulting from a basal brain tumor with involvement of the hypophysis, that there was a hypofunction of the hypophysis in this disease. Von der Helden investigated the effect of hypophysis extract upon renal action in a number of cases including diabetes insipidus, and found decreased diuresis; nevertheless he (and Humber) does not believe that the action of pituitrin is responsible for hypofunction of the hypophysis. Farni also found decreased diuresis after giving pituitrin. Lately v. Konschegg and E. Schuster proved experimentally that the pituitrin injections caused first an increased then a lessened diuresis. They as well as Graul have noticed improvement in cases of diabetes insipidus, and therefore concluded that there was a hypofunction of the gland. F. Kleeblatt reports an interesting case of diabetes insipidus following a skull injury with loss of the polyuria, also the persistent thirst and excessive perspiration, after the administration of hypophysis extract. In this case the hypophysis was intact, the cause of the condition being an irritation of the floor of the fourth ventricle. This case demonstrates that the giving of hypophysis extract, with its results on the whole clinical picture, can be used as a means of differential diagnosis in disease of the hypophysis.

L. N.

**(CORPUS LUTEUM) Menopause, Study of Vasomotor Disturbances.** Culbertson (C.) Surg. Gyn. & Obs. (Chgo.) 1916, xxiii, 667.

Fundamentally this study resolves itself into a consideration of the interrelationships of the entire system of ductless glands. The author considers that the withdrawal of the secretion of one or more of these will result in discord, just

what happens at the climacteric due to the cessation of ovarian secretion.

The varied pictures presented by patients passing through this period are explainable by the predominance or subjection of different units of the complex endocrine system. Thus many present pictures resembling hyperthyroidism, a few may suggest myxedema, and others may suggest a tendency toward acromegaly, to dystrophia adiposo-genitalis, etc. The climacteric is monoglandular only in its etiology; in its manifestations it is distinctly pluriglandular. As the ovary decreases in activity the thyroid may maintain its usual action or may vary from insufficiency to excessive action.

Culbertson intimates that in some cases the endocrine glands other than those just mentioned may be affected, the adrenals, parathyroids or even pineal may enter into the situation; in short, the menopause may present as many different aspects as there may be single glands or combinations of them. An important factor is emphasized as being nearly always present, hypertension. It was present in all but four of Culbertson's cases. While the tension is elevated it is also unstable, being affected by relatively minor influences. It presents another peculiarity, the diastolic pressure is not so proportionately high as the systolic, and the pulse pressure is characteristically irregular but increased. This it is believed may be due to overactivity on the part of the adrenals and pituitary following cessation of ovarian activity. This being the case it is suggested that corpus luteum should neutralize the pressor substances and tend to decrease tension, and, in fact, this seems to be the case for excellent results have followed this treatment in the hands of the author in many cases. He prefers an extract made from the ovaries of pregnant animals. The effect on blood pressure is not merely a consistent reduction, but the systolic and diastolic pressures tend to assume a more nearly normal relation. Emphasis is laid on the need for frequent blood pressure readings in cases of this character.

**(ADRENALIN) A Simple Procedure for Nasal Hemorrhage.** Lapat (W.) Jour. Am. Med. Assn. (Chgo.) 1916, lxvii, 1159.

Lapat reports that spontaneous recurrent epistaxis is usually due to ulceration over capillaries or a vessel in the anterior nares, but at times it is difficult to locate the precise area from which the hemorrhage comes. This difficulty may be overcome by an application of adrenalin solution to the anterior portion of the septum. This blanches the whole mucosa except at the spots which give rise to the bleeding. These then stand out clearly against the pale surface as red, circular areas. The treatment is cauterization of these spots with ninety per cent. trichloracetic acid.

**(ADRENALIN) Certain Reactions following Intravenous Injection of Salvarsan, Symptoms and Treatment.** Beeson (B. B.) Med. Rev. of Reviews (N. Y.) 1916, xxii, 881.

In the course of his consideration of the untoward incidents occasionally following Salvarsan or Neosalvarsan treatment, Beeson lends emphasis to the importance of the so-called "nitroid crises." The headache and diarrhea found in certain cases as well as serous apoplexy, indicated that there would seem to be a marked vascular dilation, and a vaso-constrictor remedy naturally would be thought of. According to Beeson adrenalin chloride solution (1:1000) is the best remedy for this condition and its effect is very satisfactory, at times even brilliant. The minimum dose should be one mil. representing one milligram of pure adrenalin. As much as four milligrams have been given in divided doses injected deeply into the gluteal muscle.

When given subcutaneously the effect is more transitory, while the intravenous route is reserved for more serious cases, as in apoplexy.

Beeson advises the injection of adrenalin ten minutes before the Salvarsan is given. The patient shortly becomes quite pale if the drug is exerting its effect and this "leuco-reaction," as it is called, is an index of the efficacy of the adrenalin in the case under treatment. The pulse is increased and there is a more or less generalized trembling, but these effects are of brief duration save perhaps of some local pain at the site of the injection.

Attention is called to the fact that flushing of the face during the injection of Salvarsan or Neosalvarsan should be an indication for stopping the procedure at once and the administration of one milligram of adrenalin.

In his conclusions Beeson heartily recommends adrenalin in all these cases. He states that it has been of real value, while the untoward effects following its use are almost nil and the benefits derived are often great.

**MAMMARY Extract in the Treatment of Menorrhagia.** Von Zelinski (W. F.) Amer. Jour. Clin. Med. (Chgo.) 1916, xxiii, 915.

Von Zelinski, of Chicago, calls attention to the therapeutic virtue which is apparently present in mammary extract, and reports favorable results following this method of treatment of preclimacteric uterine hemorrhage.

One of the cases outlined was an unmarried woman of 32 with a well defined case of dysovarism with no indication whatever of any organic change or neoplasm. The patient flowed two or three weeks at a time with intervals varying in length from two to three weeks. After approved methods of treatment had been tried and had failed—including curet-

tage and the use of styptics—mammary extract was given in five-grain doses three times a day for two periods of two weeks each. The hemorrhage was relieved "in a most satisfactory manner" and further experience confirms this author's faith in this somewhat neglected phase of organotherapy. According to von Zelinski mammary extract "is one of our best remedies for the control of functional hemorhrage due to ovarian dysfunction."

**THROMBOPLASTIN, A Further Report on its Hemostatic Value.** Hess (A. F.) Jour. Am. Med. Assn. (Chgo.) 1916, lxvii, 1717.

Hess refers to his report given about a year from the New York City Department of Health, and a little later another report on the same subject from Cronin, both published in the Journal A. M. A., on the experimental work done with thromboplastin as a hemostatic. During the past year Hess has continued his clinical experiments at the Research Laboratory, Department of Health, New York City, along this line together with laboratory tests to determine more fully the various properties of thromboplastin.

Thromboplastin solution has been supplied to several of the maternity hospitals of New York City, where it has been employed locally in cases of melena neonatorum, in bleeding from the cord, skin, mouth, vagina, etc., and also as a dressing where there was undue hemorrhage following circumcision. Thromboplastin should be applied directly to the bleeding area; clots should first be removed. Hess reports the following results from his latest investigations: Tissue juice made from brain (thromboplastin solution) has proved itself of practical value in controlling hemorrhage wherever it can reach the site of bleeding. In cases of true hemophilia it may be regarded almost as a specific hemorrhage. It is to be recommended for local use in the bleeding of the new-born, in nasal hemorrhage, and in the parenchymatous bleeding associated with various operations, etc. Where local applications fail, it should be injected into the site of hemorrhage, as in bleeding from the gums following tooth extraction. This method can readily be resorted to, as thromboplastin solution loses but little of its potency as the result of dilution and cursory boiling.

**(PITUITRIN) A Record of Personal Experience with Appendicitis.** Ehrenfried (A.) Am. Jour. Surg. (N. Y.) 1916, xxx, 289.

In his personal report Ehrenfried tells of having recently acquired the habit of using pituitrin to forestall or relieve distention following abdominal operations, and he has given as many as six or more ampuls in twenty-four hours in severe

cases, always, it seemed to him, with benefit. He has not refrained, however, in cases of severe distention from using the time honored methods of stupes, drastic enemata and gastric lavage in the rare instances when they have been indicated. Moderate stimulation has been given when necessary, and morphine has been avoided.

**(THYROID) Epilepsy.** Drysdale (H. H.) Ohio St. Med. Jour. (Columbus) 1916, xii, 802.

In the course of a general discussion on the subject, Drysdale remarks that a considerable number of cases of epilepsy present symptoms of endocrine disorder. These stand out more or less prominently and it is quite probable that the internal secretions exercise some relationship to this disease.

Among the suggestions as to treatment, Drysdale includes the administration of thyroid extract and states that in some instances this "has true therapeutic worth."

**CORPUS LUTEUM, Experience with Soluble Extract.** Royston (G. D.) Interstate Med. Jour. (St. Louis) 1916, xxiii, 1119.

Royston observed the effect of soluble extract of corpus luteum in forty-seven patients, embracing the following conditions: Nausea and vomiting of pregnancy, sexual neurasthenia, sterility, amenorrhea, oligomenorrhea, dysmenorrhea, menorrhagia, metrorrhagia, premature and artificial menopause. The majority of patients showed marked improvement; the substance acts most favorably in menstrual disturbances, which are usually permanently relieved by a few weeks' treatment. The writer recommends that patients with severe symptoms receive one to two mils. intravenously every second day.—L. F. W.

**(PARATHYROID) Research in Epilepsy.** Knox (H. A.) New York Med. Jour. 1917, cv, 406.

The author mentions the pituitary, thyroid and adrenals as factors worth considering in connection with epilepsy, and reports, in passing, on 30 cases treated with dry parathyroid gland and calcium lactate. The initial dose was 2 grains of parathyroid 3 times a day. It was increased by two additional grains per dose each month. The calcium lactate was given in saturated solution and started with a daily dose of one fluid-drachm. Fairly good results were obtained.—J. D.

**KEPHALIN to hasten Coagulation and Hemostasis after Surgical Operations.** Cecil (H. L.) Jour. Am. Med. Assn. (Chgo.) 1917, lxviii, 628.

The use of the brain phosphatid, kephalin, as a local hemostatic in genito-urinary surgery is recommended by this

author who writes of the results following this method of treatment at the Johns Hopkins Hospital.

Sufficient kephalin is dissolved in an excess of ether, about a 5 per cent. solution being made, and this concentrated kephalin solution is poured over gauze strips 6 feet long and 6 inches wide. The packs are then folded, rolled, wrapped in two muslin covers and sterilized in the steam autoclave for 10 minutes.

Kephalin coated catheters are prepared as follows: A very concentrated solution of kephalin in ether is made and smeared on the terminal 3 inches of a large gum coudé catheter, the tip end eye of the catheter being left uncoated. This coating is best secured by allowing the solution of kephalin to drop on the catheter, which is being revolved at the same time. It is then sterilized in a glass tube by steam in an autoclave. A large amount of kephalin is thus brought into direct contact with the cut surface at the vesical orifice.

The hemostatic results were referred to as "striking," as there was practically no bleeding at all where the kephalin impregnated gauze was applied to the bleeding surface.

**(ADRENALIN) L'insuffisance surrénale dans la paludisme.** Paisseau (M.) and Lemaire (G.) Presse Méd. (Paris) 1916, xxiv, 545.

The severe complications of malaria, such as coma, and the algid and choleriform symptoms, are said to be of adrenal origin. Acute degeneration of the adrenals has been revealed at autopsy in such cases. This knowledge explains many of the clinical features of malaria, especially the changes in blood pressure, lumbar and abdominal pains, vomiting, diarrhea and the severe asthenia. According to these authors adrenalin should take its place next to quinine in the treatment of the severer malarias.—H. R. H.

**[PITUITARY Therapy in Diabetes Insipidus.]** Rosenfeld (J.) Mediz. Klinik (Berl.) 1916, ix, 2521.

In a report of the January (1916) meeting of a Schleswig society Rosenfeld mentions the favorable effects of pituitary injections in diabetes insipidus. The polyuria was markedly diminished, especially when the sodium chloride intake was reduced, though with the use of salt the pituitary therapy made a great difference. Administration by mouth was just as effective as by injection. At the same meeting Frank stated that in his opinion diabetes insipidus was due to hypophyseal hyperfunction, despite the fact that in some cases good results follow pituitary therapy.—J. D.